Alcohol use in a polysubstance context: Implications for understanding the mechanisms of alcohol reinforcement

Sean Patrick Barrett, Department of Psychology, McGill University Montreal

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Acknowledgements

In completing my graduate studies I have had the opportunity to collaborate with a number of professors, graduate students and undergraduate students on various research projects. Though the specific scientific contributions made to the projects included in this thesis are acknowledged in the 'Contribution of Authors' section, a number of individuals made substantial 'non-scientific' contributions to the quality of my experience at McGill, others collaborated on projects that are not included as part of this dissertation and for some individuals the magnitude of their contributions warrants special mention.

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Contributions of Authors

"...when co-authored papers are included in a thesis the candidate must have made a substantial contribution to all papers included in the thesis. In addition, the candidate is required to make an explicit statement in the thesis as to who contributed to such work and to what extent. This statement should appear in a single section entitled "Contributions of Authors" as a preface to the thesis..."

The research presented in this thesis represents a collection of manuscripts that have either been previously published or that may be submitted for publication at a latter date. While I have made a substantial contribution to the completion of each of the manuscripts, in each case the completion of the research involved collaboration with other individuals. The relative contributions of all individuals involved in the projects described in this thesis are presented below.

For study 1, "Patterns of simultaneous substance use in Canadian rave attendees", the authors are: myself, Samantha Gross, Isabelle Garand and Dr. Robert Pihl. My involvement in the project included the conception of study, assembling research team, designed the study, contributed to design of the measure used in the study (50% contribution), collecting a portion of the data (15-20%), conducting all data analyses, and writing the paper. Samantha Gross

contributed to the project by assisting with the design of the measure (50% contribution) and by providing comments on the writing. Isabelle Garand, collected the majority of the data (80-85%), entered all of the data and assisted in the translation of the measure used into French. Dr. Pihl supervised the study and provided comments regarding the analyses and the writing. This paper is published in *Substance Use and Misuse 2005, 40 (9-10):* 1525-1538.

For study 2 "Patterns of Simultaneous Polysubstance Use in a Sample of Drug Using College Students " the authors are: myself, Christine Darredeau, and Dr. Robert Pihl. My involvement in the project included conceiving of study, assembling the research team, contributing the design of the study and the measure used in the study, analyzing all data, and writing the paper. Christine Darredeau contributed to the design of the study and the measure used in the study. Dr Pihl supervised the study and provided comments on its design as well as on the interpretation of the results. Two research assistants, Matthew Tichauer and Lana Bordy, who are not given authorship credit, collected and entered the data for this study.

For study 3 "Nicotine increases alcohol self-administration in non-dependent male smokers" the authors are: myself, Matthew Tichauer, Dr. Marco Leyton and Dr. Robert Pihl. My involvement in the project included conceiving of study, assembling the research team, designed the study, contributing to design a measure used in the study, analyzed the data, and

writing the paper. Matthew Tichauer collected and entered the data. Dr. Leyton designed computer program used in study, and provided comments on the analyses and writing. Dr. Pihl supervised the study and provided comments on its design. This paper has recently been accepted for publication in *Drug and Alcohol Dependence*.

For study 4 "The effects of dopamine precursor depletion on alcohol self-administration in men" the authors are: myself, Dr. Robert Pihl, Dr. Chawki Benkelfat, Caroline Brunelle, Dr. Simon Young and Dr. Marco Leyton. My involvement in the project included contributing to the design of the study, collecting, entering and analyzing all data related to the amino acid test days and writing the paper. Dr. Pihl contributed to the conception and design of the study, provided comments on the paper, and contributed to the supervision of the study. Dr. Benkelfat contributed to the conception and design of the study, provided medical coverage and examined all medical reports. Caroline Brunelle collected and entered all of the heart rate data. Dr. Young contributed to the conception and design of the study and was responsible for calculating the plasma amino-acid levels. Dr. Leyton contributed to the conception and design of the study, designed the computerized measure used in the study, provided comments and guidance for both the writing and analysis, and contributed to the supervision of the study.

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Abstract

Alcohol is frequently co-administered with other psychotropic substances, yet little is known about patterns of alcohol use in a simultaneous polysubstance context. In the present dissertation concomitant alcohol-drug administration is examined with an emphasis on delineating patterns of alcohol use when it is co-administered with psychostimulant drugs known to interact with neural mechanisms believed to be involved in mediating alcohol's ascending limb reinforcing effects: midbrain dopamine transmission.

In two retrospective self-report studies polysubstance users reported on their simultaneous use of drugs and alcohol. Results revealed that alcohol was commonly co-administered with various abused substances, particularly with psychostimulant drugs that are known to increase dopamine neurotransmission, and there was an identifiable pattern of administration that was characterized by initial alcohol consumption preceding repeated intermingled alcohol-psychostimulant administrations which resulted in alcohol dose escalation.

In a third study, the effects of administering the psychostimulant drug nicotine on alcohol intake was directly examined using a double-blind placebo controlled self-administration procedure. Nicotine was found to significantly increase alcohol ingestion.

In a final study we examined the effect of decreasing dopamine neurotransmission on alcohol self-administration by using a dietary manipulation that depletes the nutritional precursors to dopamine. This procedure was found to decrease alcohol consumption, an effect that was

especially evident in a subset of drinkers thought to be hypersensitive alcohol's ascending limb dopamine effects. Overall findings suggest that alcohol co-administration with psychostimulant drugs affects patterns of alcohol intake and that this may be the result of an interaction involving dopamine neurotransmission.

Résumé

Il est fréquent que l'alcool soit consommé en même temps que d'autres substances psychotropes mais on connaît peu de choses sur ces pratiques de consommation simultanée d'alcool et de substances multiples. Cet exposé s'intéresse à l'administration simultanée d'alcool et d'autres drogues en s'appliquant particulièrement à décrire les pratiques de co-consommation d'alcool et de psychostimulants agissant sur les mécanismes neurologiques par l'entremise desquels on croit qu'interviennent les effets renforçateurs de la phase d'augmentation de la quantité d'alcool dans le sang: il s'agit de la transmission de dopamine dans le mésencéphale.

Dans deux enquêtes réalisées a posteriori, des consommateurs de drogues multiples décrivent leurs habitudes de consommation simultanée de drogues et d'alcool. Les résultats confirment que l'alcool est couramment consommé en même temps que des drogues diverses connues pour augmenter la neurotransmission de dopamine. D'autre part, on identifie une pratique de consommation consistant en une prise initiale d'alcool suivie de consommations alternées et répétées d'alcool et de psychostimulants dont le résultat est une consommation accrue d'alcool.

Dans une troisième étude, les effets de l'administration d'un psychostimulant, la nicotine, sont examinés au moyen d'un protocole d'auto-administration en double aveugle avec placebo. Il apparaît que la nicotine a pour effet d'augmenter la consommation d'alcool.

Une dernière étude examine l'effet de la réduction de la neurotransmission de dopamine en utilisant un artifice alimentaire qui permet de réduire les précurseurs nutritionnels de la dopamine. On observe que cette procédure réduit la consommation d'alcool, cet effet étant particulièrement manifeste pour un sous-groupe de consommateurs qu'on estime très sensibles à la dopamine en phase ascendante de la quantité d'alcool dans le sang.

Les résultats de manière générale suggèrent que l'administration d'alcool avec des psychostimulants affecte les pratiques de consommation d'alcool et que ceci pourrait être le résultat d'une interaction impliquant la neurotransmission de dopamine.

1. Introduction

Substance use disorders represent the most prevalent form of adult psychopathology (e.g. Somers et al., 2004) and are associated with a variety adverse health, economic and social outcomes (e.g. Andin-Sobocki, 2004) . Conservative estimates place the annual societal costs associated with alcohol and drug use in the hundreds of billions of dollars (e.g. Rice, 1999), yet substance use disorders remain relatively poorly understood as well as notoriously difficult to treat (e.g. McLallan & Meyers, 2004). One issue that may confound our understanding of addictive processes is the tendency for drug users to administer multiple substances concomitantly, a phenomenon known as simultaneous polysubstance use.

Although evidence suggests that substance users frequently co-administer multiple substances, most drug-related research tends to focus on examining single substances under highly controlled conditions rather than delineating the specific ways that drug users typically use their substances. A growing body of literature has documented high rates of simultaneous polysubstance use across several different drug using populations including alcoholics (Staines et al., 2001; Martin et al., 1996a), college students (e.g. Webb et al., 1995), rave attendees (e.g. Winstock et al., 2001; Tossmann et al., 2001) and adolescents (e.g. Martin et al., 1993a; 1996b; Collins et al., 1998), as well as across users of various substances including alcohol (e.g. Martin et al., 1996a; Staines et al., 2001), cannabis (e.g. Earleywine & Newcomb, 1997),

cocaine (Leri et al., 2004), heroin (Darke & Ross, 1997), hallucinogens (Barrett et al 2000 see Appendix 1), benzodiazepines (Ross & Darke, 2000) and 3,4-methylenedioxymethamphetamine (MDMA; ecstasy) (e.g. Tossmann et al., 2001). However, to date most studies that have described trends in simultaneous polysubstance use have primarily focused on whether or not two or more target substances have been used together (e.g. Leri et al., 2004; Martin et al., 1996a) and little is known about the order and patterns of administration of substances when they are used together or their relative doses. Given that many abused substances appear to be routinely co-administered, delineating the patterns and consequences of concurrent multiple substance use may have important implications for understanding addictive processes.

Substances that are frequently co-administered with each other may not be haphazardly combined but may rather be co-administered because their combination enhances certain desirable effects, diminishes certain undesirable effects and/or because they interact with central mechanisms that regulate the use of one another (e.g. Leri et al., 2003). If this is the case, then the administration pattern of a particular substance might largely depend on what other substances are used and a drug's abuse liability may change depending on the other substance(s) being administered. Moreover because experimental evidence suggests that the way that certain commonly co-administered drugs interact may depend on factors such as their relative order (s) of administration

(e.g. Perez-Reyes, 1994; Clemens et al., 2005) and doses (e.g. Perez-Reyes et al., 1992), it is also possible that polydrug users preferentially co-administer some substances in a particular order and particular quantities so that they can achieve desirable results.

Most laboratory studies that examine the concurrent use of multiple substances tend to compare the effects associated with the solitary administration of each of the substances with those of two or more substances combined (Earleywine & Newcomb, 1997). In such paradigms many drug-related factors are usually meticulously controlled for including the timing, order and amount of each dose to be administered, and additional assurances are made that participants have remained abstinent from all substances that are not under direct investigation (e.g. Hernandez-Lopez et al., 2002; Kouri et al., 2004). While such efforts to achieve experimental control are laudable, this approach may fail to yield ecologically valid results if the administration parameters and substances chosen by the experimenter markedly differ from those typically used in a more 'natural' setting.

In the present dissertation patterns of simultaneous polysubstance use are examined using a variety of methods with an emphasis on how alcohol is used with various commonly abused psychstimulant substances. Alcohol has been identified as one of the most frequently co-administered substances with various stimulant drugs including tobacco (e.g. Batel et al., 1995), amphetamine (e.g. Molina & Jejurika, 1999), cocaine (e.g. Pennings et al.,

2002), and methylphenidate (e.g. Barrett et al., 2005, see Appendix 2) and previous research suggests that alcohol co-administration with each of these drugs may result in desirable subjective changes (e.g. Perez-Reyes & Jeffcoat, 1992; Mendleson et al., 1995; Perkins et al., 1995; Barrett & Pihl, 2002, see Appendix 3). However little is currently known about the temporal sequence of alcohol-stimulant administration, the degree to which concurrent stimulant use changes alcohol administration patterns or the degree to which other substances are concomitantly used with alcohol-stimulant combinations.

Because various psychostimulant substances are known to interact with central dopamine (DA) systems (e.g. Wise, 1996) that have been implicated in mediating alcohol self-administration (e.g. Leyton et al., 2000a; Enggasser & de Wit, 2001; Modell et al., 1993), an evaluation of how these substances affect alcohol intake may provide additional insight into alcohol's reinforcement mechanisms. Moreover because alcohol's neurochemical (e.g. Ollat et al. 1988) and subjective (e.g. Martin et al. 1993b) effects are known to be biphasic, an examination of the timing of stimulant co-administration may provide information about the nature of the interaction and motives of simultaneous use. Finally if psychostimulant co-administration does result in systematic changes in alcohol intake patterns and these are related to a particular neurochemical effect, then one would expect manipulations that produce opposite neurochemical actions to have opposite effects on alcohol ingestion.

2. Literature Review

The focus of this literature review will be research that has examined the intake patterns, effects and/or mechanisms associated with the concomitant administration of alcohol and various psychostimulant drugs. Because the primary goal of this dissertation is to better understand how and why humans use drugs and alcohol in the ways that they do and each of the studies included in this dissertation used human participants, whenever possible an emphasis will be placed on reviewing the relevant findings from human studies. However, animal studies are also cited in some instances especially when the findings are seminal to our understanding of a given phenomenon. This is particularly true in sections that review the neurochemical effects of the substances (Sections 2.33-2.35) and when animal studies are cited this will be clearly indicated in the text.

For the purposes of this dissertation the term 'psychostimulant' will be used to describe all substances whose primary psychoactive effects are to stimulate psychological and sensory-motor functioning and that meet the *Diagnostic and Statistical Manual of Mental Disorders*, IVth edition (DSM-IV), classification criteria for being a drug of abuse and/or dependence. This definition includes substances such as tobacco (nicotine), cocaine, amphetamine and methylphenidate and the reinforcing properties of each of these substances is believed to mediated by a common central DAergic action (please see section 2.33 below). Other substances with stimulant properties

such as caffeine, that do not meet the DSM IV's classification criteria as a substance of abuse or dependence are not included in this operational definition and findings from animal studies suggest that such substances are often devoid of significant DAergic effects (Cauli & Morelli, 2005).

2.1 Prevalence & Patterns of Alcohol-Psychostimulant Co-administration

A growing body of evidence suggests that alcohol is commonly co-administered with a variety of psychostimulant drugs and that in some cases the tendency to co-administer these substances may be especially prominent among individuals dependent on one (or more) of the substances (e.g. Dawson et al., 2000; Pennings et al., 2002). Previous research detailing the patterns and prevalence of alcohol co-administration with specific psychostimulant substances is outlined below.

2.11 Alcohol and Tobacco

Perhaps the most commonly co-administered substance with alcohol is tobacco (e.g. Batel et al., 1995; Dierker et al., 2005). The prevalence of tobacco smoking among alcoholics is thought to be as high as 90% compared to a general population rate of less than 30% (e.g., Sobell et al., 1990; Romberger & Grant, 2004) and it is estimated that smokers are 50% more likely to drink regularly than non-smokers (Kozlowski & Ferrence, 1990). In addition the strength of the alcohol-tobacco relationship appears to be proportional to the extent of use of either substance (e.g. Dierker et al., 2005;

Bien & Burge, 1990) with binge drinkers being more likely to smoke than non-binge drinkers (Tucker et al., 2002), heavy smokers reporting greater alcohol consumption than occasional smokers (Resnicow et al., 1999) and alcoholics smokers using more cigarettes per day than non-alcoholic smokers (Dawson, 2000). Moreover while smokers appear to be more likely to drink and drinkers more likely to smoke evidence suggests that the two behaviours often co-occur during the same session. For example, both college students (Dierker et al., 2005) and adolescents (Duhig et al., 2005) are more likely to drink on days that they smoke and to smoke on days that they drink and across tobacco using populations, smoking frequently occurs during the course of a drinking session (e.g. McKee et al., 2004; Batel et al., 1995). There is also evidence that alcohol consumption acutely increases cigarette smoking (e.g. Griffiths et al., 1976; Mello et al., 1980; Keenan et al., 1990) although little is known about the degree to which acute tobacco smoking increases alcohol consumption.

2.12 Alcohol and Cocaine

Alcohol has also been identified as being one of the most commonly co-administered substances with cocaine. In a population-wide study it was estimated that approximately 80% of the 5 million Americans who had used cocaine over the preceding month had simultaneously administered alcohol (Grant & Hartford, 1990). It is also estimated that up to 90% of cocaine abusers have simultaneously used alcohol with cocaine (e.g. Wiseman & Mcmillan, 1996) and there appears to be a high rate of co-occurrence of

alcohol and cocaine-related disorders. Cocaine has been identified as the most commonly co-administered illicit substance with alcohol among treatment seeking alcoholics (Martin et al., 1996a; Staines et al., 2001) and an analysis of consecutive admissions of cocaine dependent individuals revealed that 61% were also alcohol dependent (Heil et al., 2001). In addition, a study of alcoholics seeking treatment 40% reported cocaine use during the preceding year (Walsh et al., 1991) suggesting a rate of cocaine use among alcoholics that is seven to eight times greater than that seen in the general population (Pennings et al., 2002). Moreover evidence also suggests a poorer prognosis for treatment in cocaine addicts who co-administer alcohol (McKay et al., 1999) as well as in alcoholics who co-administer cocaine (Carroll et al., 1998), with the use of one substance being associated to relapse in the use of the other. Although evidence suggests that cocaine and alcohol are frequently co-administered and that this may be related to dependence on one or both of the substances, currently very little is known about how the two drugs are used together during the same session, or the degree to which the use of one of these drugs influences the administration of the other. It has been suggested that cocaine users may frequently administer alcohol at or near the end of a cocaine administration session in an effort to 'come down' from the effects of cocaine (Maguara & Rosenblum, 2000). Conversely alcohol consumption has been demonstrated to increase the reinforcing value of cocaine in non-dependent participants offered a post-alcohol choice between cocaine and a monetary reward (Higgins et al., 1996), suggesting that alcohol use might increase the

probability of cocaine use. Finally, although evidence also suggests that other psychoactive substances might often be simultaneously co-administered with cocaine and alcohol (Martin et al., 1996a) the degree to which these affect patterns of cocaine-alcohol use remains unknown.

2.13 Alcohol and Other Psychostimulants

While the lion's share of the research that has examined alcohol co-administration with stimulant drugs has focused on tobacco and cocaine, alcohol also appears to be among the most frequently co-administered substances with various other stimulants as well. For example there is growing evidence that alcohol is also commonly simultaneously used with the prescription psychostimulant medication methylphenidate. In a study of the drug taking patterns of intravenous methylphenidate abusers 41% reported that they concomitantly co-administered alcohol (Parran & Jasinki, 1991) and we recently found that 71% of recreational methylphenidate users reported lifetime simultaneous alcohol use while 34% reported co-administering alcohol during their most recent methylphenidate use (Barrett et al., 2005, see Appendix 2). Moreover a report of emergency department statistics further attests to the high prevalence of alcohol-methylphenidate co-administration with 553 alcohol-methylphenidate related emergency episodes reported in 1997 and 422 being reported in 1999 (DAWN 1997; 1999 as cited in Patrick et al., 2005). Finally, while I am unaware of any studies that have directly assessed the prevalence or patterns of simultaneous alcohol-amphetamine co-

administration, alcohol has been identified as the drug most frequently associated with complications arising from methamphetamine use (e.g. Mendelson et al., 1995; Yamamura et al., 1991) and concomitant alcohol use has been implicated in approximately 30% of methamphetamine related deaths (Molina & Jejurika, 1999).

Although alcohol appears to be commonly co-administered with a variety of abused stimulant drugs and at least in some cases alcohol-stimulant co-administration appears to be associated with higher levels of dependence (e.g. Dawson et al., 2000; McKay et al., 1999), little is known about how alcohol and stimulants are used together or the degree to which concomitant administration affects patterns of use. Nevertheless, a growing body of evidence suggest that psychostimulant-alcohol co-administration may result in an alteration in subjective effects, a factor that could contribute to their propensity to be simultaneously used (e.g. Cami et al., 1998; Perkins et al., 1995; Barrett & Pihl 2002, see Appendix 3). The section below reviews the literature on the phenomenological effects associated with alcohol-psychostimulant co-administration.

2.2 Phenomenology of Alcohol-Psychostimulant Co-administration

Despite the high prevalence of alcohol-tobacco co-administration little is known about the subjective effects associated with it. In a single placebo controlled study alcohol was reported to increase the level of 'satisfaction' associated with consumption of nicotine containing cigarettes (Rose et al.,

2002), however the effects of other subjective parameters are not reported. Similarly in a retrospective study it was reported that smokers recalled experiencing increased 'pleasure' from smoking when tobacco was used with alcohol (McKee et al., 2004). Other investigations that have examined the combined effects of alcohol with nicotine, the alkaloid associated with tobacco's stimulant and reinforcing properties (e.g. Domino, 1998) suggest that co-administered nicotine alters certain subjective effects of alcohol. For example intranasal nicotine administration has been shown to increase alcohol-related stimulation when blood alcohol levels are rising and decrease alcohol-related sedation when blood alcohol levels are falling (Perkins et al., 1995) while transdermal nicotine administration has been shown to increase alcohol-related euphoria (Kouri et al., 2004).

Interestingly investigations that have examined the subjective responses to the combined effects of alcohol with cocaine (e.g. Mannelli et al., 1993, Cami et al., 1998) or with amphetamine (Mendelson et al., 1995) under controlled conditions have identified similar alterations to subjective effects as those observed with alcohol and nicotine. The combination of alcohol and cocaine has been reported to significantly increase euphoric and stimulant-like effects such as 'high' (e.g. Perez-Reyes & Jeffcoat, 1992) and 'euphoria' (e.g. Farre et al., 1993) relative to either substance alone as well as to decrease alcohol-related sedation and/or sense of drunkenness (e.g. Pennings et al., 2002) relative to alcohol alone. Similarly the subjective effects of methamphetamine-alcohol combinations were characterized by an increase in

stimulant-like effects as well as a diminished sense of alcohol-related intoxication (Mendelson et al., 1995). Moreover although the subjective responses associated with methylphenidate-alcohol co-administration have not been examined under controlled conditions, in retrospective reports the combined effects have been described as producing a desirable effect characterised by increased euphoria and energy and/or a diminished sense of drunkenness (Barrett & Pihl, 2002, see Appendix 3). While these findings should be interpreted with caution due to the lack of control of or information about participants' use of other substances, similarities between these self-reports and objectively measured subjective effects associated with alcohol co-administration with other stimulant drugs are nonetheless striking.

The evidence described above suggests that when alcohol is co-administered with various psychostimulant drugs it tends to result in a similar phenomenological effect that is characterized by heightened euphoria and/or stimulation as well as a decreased sense of sedation and drunkenness, raising the possibility that a common pharmacological action may underlie these effects. Possible mechanisms involved in alcohol-psychostimulant interactions are described below.

2.3 Alcohol-Psychostimulant Interactions

Although a number of factors might contribute to the propensity to simultaneously use alcohol with different psychostimulant substances, such as various personality variables (e.g. Brunelle et al., 2004, see Appendix 4), the

relative availability of the substances and/or the presence or absence of substance using peers (e.g. Sloboda, 2002), it is highly probable that the behavioural and/or subjective effects associated with the co-administration of these drugs are paramount to their simultaneous use (e.g. Leri et al., 2004;) and that such effects are the result of specific pharmacological interactions.

Pharmacological interactions can be either pharmacokinetic or pharmacodynamic in nature. Pharmacokinetic interactions are those in which the presence of one substance affects the absorption, distribution, metabolism or excretion of another substance resulting in a relative change in the concentration of the substance in the blood at a given time point (e.g. Weatherman & Crabb, 1999) and in the case of alcohol-psychoactive drug interactions this generally results in a change in the availability of the substance to exert its effects in brain. In contrast pharmacodynamic interactions refer to changes in the way that substances affect different systems in the body that are independent of changes in the substances' relative concentrations and in the case of alcohol and other psychoactive substances many of these interactions commonly occur in the brain and involve additive, antagonist or synergistic effects at specific neurotransmitter sites hypothesized to be involved in the production of the substances' subjective or reinforcing effects (e.g. Weaterman & Crabb, 1999).

2.31 Pharmacokinetics

The presence (or absence) of a pharmacokinetic interaction is usually directly assessed in the laboratory by measuring quantities of the substance in the plasma, following the administration of fixed doses of each of the drugs combined with each other as well as with a placebo (e.g. Mendelson et al., 1995). In many cases, the nature of a particular pharmacokinetic interaction will largely depend on factors such as the relative quantities of each the substances, their routes and orders of administration and the degree to which other substances are also present (e.g. Perez-Reyes 1994; Perez-Reyes et al., 1992). However, because most studies that have examined possible pharmacokinetic interactions involving alcohol with other substances have done so using a very limited range of conditions and preclinical data on the ways that alcohol and other drugs are co-administered is currently lacking, very little is known about how pharmacokinetic factors may contribute to the simultaneous use of alcohol with other substances. Nevertheless there is currently evidence to suggest that alcohol co-administration with some, though not necessarily all psychostimulant drugs results in significant pharmacokinetic interactions, at least under certain conditions.

Several studies have examined possible pharmacokinetic interactions between cocaine and alcohol (e.g. Pennings et al., 2002; Cami et al., 1998). When cocaine is administered either at the same time as or following alcohol, plasma cocaine levels have been demonstrated to increase by up to 30%, while

blood alcohol levels appear to remain relatively unaffected (Farre et al., 1993; Farre et al. 1997; Perez-Reyes & Jeffcoat, 1992; Cami et al., 1998.). Interestingly however, when cocaine is administered prior to alcohol there is no evidence of alterations to either plasma cocaine or alcohol levels (Perez-Reyes 1994). While these discrepant effects have been hypothesized to be related to competitive inhibition of a hepatic esterase involved in cocaine metabolism when alcohol is administered prior to or concurrently with cocaine (Pennings et al., 2002) they also highlight the importance of documenting the ways in which the substances are co-administered by drug users themselves. For example findings of altered cocaine pharmacokinetics when it is administered following alcohol may be of limited clinical relevance if drug users routinely only administer alcohol after using cocaine. In addition to (sometimes) increasing plasma cocaine levels, alcohol-cocaine co-administration has also been demonstrated to result in the production of a novel psychoactive metabolite cocaethylene. Cocaethylene has been demonstrated to produce similar behavioural and subjective effects to cocaine in humans (e.g. Cami et al., 1998) and appears to be produced irrespective of the order of cocaine and alcohol administration (Perez-Reyes, 1994). Although only a fraction (15-17%) of cocaine is believed to be converted to cocaethylene (Harris et al., 2003) and its plasma concentrations tend to be relatively low relative to cocaine (e.g. Cami et al., 1998), cocaethylene has a slower rate of clearance from the brain (e.g. Pennings et al., 2002) and it is possible that this metabolite contributes to the subjective, behavioural or

physiological effects associated with alcohol-cocaine co-administration (e.g. Cami et al. 1998).

Pharmacokinetic interactions between alcohol and tobacco have not (to my knowledge) been systematically investigated, and the few studies that have examined alcohol-nicotine interactions have produced inconclusive results. Although evidence suggests that nicotine may alter mechanisms involved in hepatic alcohol metabolism (Schoedel & Tyndale, 2003) as well as rates of gastric emptying (Gritz et al., 1988), factors that could affect alcohol distribution and absorption, in animal studies alcohol and nicotine have failed to alter each other's pharmacokinetic properties (Collins et al., 1988). Moreover in humans, studies that have examined alcohol-nicotine pharmacokinetic interactions suggest that alcohol does not appear to affect nicotine metabolism (Benowitz et al., 1986) while nicotine has not been shown to produce consistent effects on alcohol's pharmacokinetics (Perkins et al. 1995; Kouri et al. 2004).

Potential pharmacokinetic interactions between alcohol and amphetamine have been examined in two studies that have produced mixed results. While the pre-administration of alcohol increased the bioavailability of a moderate dose of oral d-amphetamine (0.18 mg/kg) it had no effect on the pharmacokinetics of a lower dose (0.09 mg/ kg) (Perez-Reyes et al., 1992). Moreover in a study examining alcohol-methamphetamine interactions, intravenous methamphetamine administered following alcohol consumption

did not significantly alter the pharmacokinetic properties of either substance, with the exception of decreasing the apparent volume of distribution of methamphetamine, an effect of unknown significance (Mendelson et al., 1995).

There is also evidence that alcohol-methylphenidate co-administration may result in significant pharmacokinetic interactions. Alcohol co-administration has been reported to increase plasma concentrations of methylphenidate (administration order and dosages were not reported) (Patrick et al., 2005) as well as result in the production of a novel metabolite ethylphenidate (Markowitz et al., 2000) that, like cocaethylene, is produced in relatively low concentrations, but might contribute to the combined effects of the drugs (Markowitz et al., 2000; Patrick et al., 2005).

While evidence suggests that concomitant alcohol administration may result in significant pharmacokinetic interactions with cocaine, amphetamine and methylphenidate, at least under some conditions, there is currently little data to support a significant pharmacokinetic interaction between alcohol and tobacco. It is important to note, however, that because most studies have used a limited range of substances, doses and administration parameters, and descriptive data on how many of the substances are normally used is lacking, the results should be interpreted with caution.

2.32 Pharmacodynamics

Unlike pharmacokinetic interactions which are typically directly measured, pharmacodynamic interactions between psychoactive substances are usually inferred from the behavioural/subjective changes that result from co-administering substances known to affect common neurotransmitter systems. Support for the involvement of a specific neuropsychopharmacological action in the production an effect might include 1) observations that drugs with similar actions on the substrate(s) hypothesized to be involved produce similar behavioural/subjective changes when co-administered with the target substance; 2) observations that treatments with opposite actions on the substrate(s) result in opposing behavioural and/or subjective changes; and 3) evidence that behavioural and/or subjective changes cannot be attributed to actions on substrate(s) other than those hypothesized to be involved.

In the case of alcohol-psychostimulant interactions, it is proposed that a common DAergic substrate may be involved in the production of significant pharmacodynamic interactions that contribute to the propensity for alcohol to be co-administered with these drugs. In the section below evidence linking particular psychostimulant and alcohol-related effects to this substrate will be reviewed and because each of the drugs reported is believed to exert a similar effect on this substrate, it is proposed that examining the effects of alcohol-co-administration with each of these substances may help delineate the alcohol-related effects that are associated with DA.

2.33 DAergic Effects of Abused Stimulants

The abuse potential of psychostimulant drugs is believed to be associated with their ability to increase extracellular levels of DA in mesocorticolimbic regions (e.g. Wise & Bozarth, 1987; DiChiara & Imperato, 1988; Wise, 1996; Koob, 2000). Cocaine and methylphenidate achieve their DAergic effects through a common mechanism by binding to the DA transporter in the presynaptic cell membrane, thereby inhibiting DA reuptake (e.g. Volkow et al., 1995). These drugs display similar affinities for DA transporters (Gatley et al., 1996; Volkow et al., 1998), their administration lead to comparable changes in synaptic DA levels (Kuczenski & Segal, 1997; Volkow et al., 1999a) and although cocaine is also believed to have a significant affects on serotoninergic neurotransmission (e.g. Segal & Kucezenski, 1999) methylphenidate's central effects appear to be relatively DA specific (e.g. Fleckenstien et al. 1999; Segal & Kucezenski, 1999), and as a result the similarities in the behavioural effects of these two drugs can be inferred to be associated with their DAergic properties. Like cocaine and methylphenidate, both amphetamine and nicotine administration also results in increased in synaptic DA levels; however these drugs appear to achieve their DAergic effects through different mechanisms. While amphetamine increases DA neurotransmission both by inhibiting reuptake as well as by stimulated of DA release from the presynaptic ending (e.g. Segal & Kuczenski, 1999), nicotine is believed to increase DA release via stimulation of nicotinic receptors located on DA containing cells (e.g. Corrigall et al., 1994; Pontieri et

al., 1996, Pidopichko et al., 1997). Moreover although evidence suggests that the magnitude of nicotine's DAergic effects is not as great as for other psychostimulants in either laboratory animals (e.g. Yanagita et al., 1995; Tsukada et al., 2002) or in humans (Barrett et al., 2004; see Appendix 5), recent animal findings suggest that nicotine administration may facilitate the DAergic response to other reinforcers (Rice & Craig, 2004; Zhang & Sulzer, 2004).

While there appears to be some heterogeneity in mechanisms through which cocaine, methylphenidate, amphetamine and nicotine increase synaptic DA levels, in each case these DA effects are thought to be critical to the substance's reinforcing effects (e.g. Wise & Bozarth, 1987; DiChiara et al., 1998). For example, in laboratory animals a disruption of DA function has been demonstrated to reduce cocaine (e.g. Stewart & deWit, 1987), amphetamine (e.g. Wise 1996) and nicotine (Corrigall et al., 1992) intake as well as prevent the locomotor stimulant effects associated with cocaine (e.g. Wise, 1998; Koob; 2000), methylphenidate (Mithani et al., 1986) amphetamine (e.g. Wise, 1998) or nicotine (e.g. Clarke et al. 1988; Louis & Clarke 1998) administration, while human functional neuroimaging studies in humans have linked amphetamine (Martinez et al., 2003; Drevets et al., 2001), methylphenidate (Volkow et al. 1999) and nicotine (Barrett et al., 2004; Appendix 5) induced changes in DA to the subjective hedonic properties of the drugs.

2.34 DA and Alcohol

Although alcohol is known to affect numerous neurochemicals including acetylcholine, DA, GABA, glutamate, norepinephrine and serotonin, its subjective effects and reinforcing properties are thought to be largely mediated by DA and GABA (e.g. Fromme et al., 2003). Each of these neurotransmitters has been hypothesized to be involved in different aspects of the alcohol response and in both cases their effects are believed to be time and dose dependent (e.g. Ollat et al., 1988). Like various psychostimulant drugs, alcohol administration increases DA neurotransmission in mesocorticolimbic regions in both laboratory animals (e.g., Samson et al., 1992; Koob et al. 1998) and humans (Boileau et al., 2003) and this action is believed to be involved in its reinforcing properties (Di Chiara & Imperato, 1988; Koob et al. 1998). Animal studies indicate that alcohol's DAergic effects appear to predominantly occur during the ascending limb of the blood alcohol concentration (BAC) curve when blood alcohol levels are rising (e.g. Marinelli et al., 2003) and alcohol-related DA transmission has been proposed to mediate alcohol's stimulant effects (e.g. Enggasser & DeWit, 2001) and self-administration (e.g. Modell et al., 1993) in humans. In contrast, GABA is thought to mediate alcohol's descending limb sedative and anxiolytic actions (e.g. Pihl & Peterson, 1995) and with cumulative doses alcohol-induced GABAergic

activation may inhibit alcohol-related DAergic effects (e.g. Ollat et al., 1988; Gerasimov et al., 1999).

2.35 Altering Alcohol's DA-related effects

In rodents alcohol self-administration has been demonstrated to be time-locked to increases in DA neurotransmission (Weiss et al., 1992) and DA antagonists have been demonstrated to attenuate voluntary alcohol intake (e.g. Rassnick, 1992; Files et al., 1998). In humans, functional neuroimaging studies demonstrate that acute ingestion of alcohol increases DA release (Boileau et al., 2003) while decreasing DA neurotransmission leads to reductions in alcohol self-administration (Leyton et al., 2000a; Enggasser & de Wit, 2001, Modell et al., 1993) and alcohol-related stimulation (Enggasser & de Wit, 2001). Although evidence indicates that decreasing DA neurotransmission reduces alcohol self-administration and certain alcohol related effects, less is known about how these are affected by selective increases in DA activity. Animal models that have examined the effect of DA agonists on alcohol administration have produced equivocal results, with some studies finding increased levels of ethanol intake (e.g. Samson et al., 1993) and others reporting decreases (Hodge et al., 1997). In human studies alcohol co-administration with any of nicotine (Pekins et al., 1995), cocaine (Farre et al., 1993), methamphetamine (Mendelson et al., 1995) or methylphenidate (Barrett & Pihl, 2002, see appendix 3) have been reported to be predominantly associated with increased stimulant-like effects and diminished sedation, but

the effect of these substances on alcohol intake have not been systematically investigated.

2.36 Alcohol Administration and DA Sensitivity

A growing body of evidence suggests that many problematic drinkers as well as individuals at risk for developing alcohol related problems may experience exaggerated ascending limb DA effects from alcohol. For example, alcoholics, heavy drinkers, and individuals with a family risk for alcoholism display greater ascending limb subjective stimulant effects following alcohol administration relative to non-alcoholics, light drinkers and individuals with no family history of alcoholism respectively (Thomas et al., 2004; Holdstock et al., 2000; King et al., 2002; Elbridge et al., 2003). Moreover, in addition to subjective stimulation problematic/at risk drinkers also appear to exhibit a heightened physiologic response to alcohol during the ascending limb of the BAC as indexed by cardiac responsivity to acute alcohol ingestion (e.g. Conrod et al., 2001). It has been proposed that a heightened heart-rate (HR) response to alcohol is a peripheral marker to identify individuals that exhibit heightened alcohol-related DA transmission (Brunelle et al., 2004, see Appendix 4; Conrod et al., 2001) and this hypothesis is supported by findings that alcohol-induced cardiac effects are proportional to both DA release (Boileau et al., 2003) and alcohol-related stimulant effects (Brunelle et al., 2005) as well as by evidence that treatments that directly (Enggasser & de Wit,

2001) or indirectly (McCaul et al., 2001) disrupt DA function attenuate alcohol-induced HR increases. Interestingly evidence also suggests that co-administration of alcohol with any of cocaine (e.g. Cami et al., 1998), amphetamine (e.g. Mendelson et al., 1995) or nicotine (e.g. Perkins et al., 1995) produces HR increases that are greater than those associated with the solitary administration of the substances, although the mechanisms mediating such changes have yet to be determined.

2.4 Current investigations

The present series of studies examines alcohol-psychostimulant co-administration as well as the role of DA in alcohol self-administration from a variety of perspectives. First because descriptive data on the way alcohol and psychostimulants are used together is lacking, and such information is necessary both for designing ecologically valid studies and for interpreting the current literature, studies 1 & 2 examine polysubstance use patterns using structured interview techniques, with an emphasis on delineating the order and amounts of all substances consumed. It was expected that alcohol co-administration with psychostimulants would follow an identifiable pattern and, because stimulants increase DA transmission, that their co-administration would be found to be associated with increased alcohol intake. Second, because the effects of stimulant co-administration on alcohol intake have yet to be directly investigated in humans, in study 3 the effects of simultaneous nicotine use on alcohol self-administration was examined in a laboratory

setting using a double-blind placebo controlled study. Finally because DA has been linked to alcohol self-administration (e.g. Koob et al. 1998) and evidence suggests that certain individuals may be more sensitive to alcohol's DA-related effects (e.g. King et al., 2002 ; Conrod et al., 2001), in study 4 the effects of selectively decreasing DA neurotransmission on alcohol intake was investigated in a heterogeneous sample of drinkers, using the acute phenylalanine-tyrosine depletion method. This method decreases DA neurotransmission through a dietary manipulation and Appendix 6 provides a detailed description of this technique in a recently published review article about this method (Barrett & Leyton, 2004, see Appendix 6).

3. Prologue to Study 1

The first paper presented in this dissertation is a reproduction of the manuscript "Patterns of Simultaneous Polysubstance Use Patterns in Canadian Rave Attendees" that was published in 2005 in *Substance Use and Misuse 40, 1525-1537.* This study was in part a follow-up to a previous investigation that examined the drug use patterns in rave attendees (Gross et al., 2002; please see Appendix 7), and its purpose was to delineate specific patterns of simultaneous polysubstance use in this population. Despite its focus on rave specific substance use, I decided to include it as part of this dissertation because: 1) it uses a method I helped develop to the delineate specific patterns of polysubstance use that are related to a particular instance; 2) it examines the reliability of drug users' recollections of the type, order and amount of all substances used on a particular occasion; and 3) alcohol-specific patterns of simultaneous substance are addressed.

Patterns of Simultaneous Polysubstance Use in Canadian Rave Attendees

Sean P. Barrett[1], Samantha R. Gross[2], Isabelle Garand[1], Robert O. Pihl[1]

[1]Department of Psychology, McGill University, Montreal Canada

[2]National Addiction Centre, Institute of Psychiatry, London United Kingdom.

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3.1 Abstract

The aim of this study was to examine rave-related polydrug drug use and to determine if patterns of substance use were associated with previous rave attendance. One hundred and eighty-six rave attendees (50% female) representing wide range of ages (16 to 47 years; mean=23.5, sd=5.15) and levels of rave attendance experience (1 to 400 events) completed structured interviews in Montreal, Canada between November 2002 and September 2003 about their rave attendance patterns and their use of various licit and illicit substances at the most recently attended event. On average participants reported using 2.5 different psychoactive substances (excluding tobacco) at the most recent event attended. Cannabis, alcohol, MDMA (ecstasy), amphetamine, cocaine, ketamine and GHB were the most frequently reported substances and details about their orders of administration, dosages and patterns of co-administration are presented and discussed. The total lifetime number of raves attended by participants varied considerably (mean=48.6; sd=69.7; median=25) and there was a positive correlation between the number events attended and number of substances used at the most recent event attended ($p<.001$). Analyses revealed individuals reporting the use of ketamine, GHB and/or cocaine at the most recent event had attended significantly more events than nonusers even when controlling for various demographic variables. A subset of respondents (n=27) completed a second interview to determine the reliability of their responses. Results indicated that

respondents could reliably recall details about which drugs were used, the total doses administered as well as order of drug administration.

Key words: polysubstance use, rave, MDMA, amphetamine, GHB, ketamine, cocaine, substance use patterns, substance use trends

3.2 Introduction

Numerous investigations conducted worldwide have documented high rates of illicit substance use among rave attendees (Lenton et al., 1997; Winstock et al., 2001; Gross et al., 2002; Tossmann et al., 2001; Forsyth, 1996). Drugs such as 3,4-methylenedioxymethamphetamine (MDMA or ecstasy), amphetamine and cannabis have consistently been identified as being frequently used within this population (Lenton et al., 1997; Gross et al.,2002; Tossman et al., 2001) and recent reports indicate that other substances such as gamma-hydroxybutyrate (GHB) and ketamine (e.g. Freese et al., 2002) are increasing in popularity. Evidence also suggests that rave-related drug use often occurs in a polysubstance context. For example, in an Australian sample, 80% of rave attendees reporting any using substance used multiple substances (Lenton et al., 1997) while 66% of respondents in a Scottish study (Riley et al., 2001) reported polysubstance use. This trend toward polysubstance use has generated concern due to the possibility that simultaneous multiple substance administration results in increased toxicity (e.g. Schifano et al., 2003).

Despite the apparent prevalence and potential adverse consequences associated with polysubstance administration, little is known about the specific patterns of rave-related multiple drug use. In a study of British ecstasy users Winstock et al. (2001) documented high levels of lifetime ecstasy co-administration with various licit and illicit substances including alcohol, cannabis and amphetamines. However, this study did not provide information

about *what substances* were used concurrently with ecstasy at raves or on any particular occasion. In a recent American study, Fendrich et al. (2003) reported high levels of concurrent drug co-administration among 'club' drug users (identified as MDMA, ketamine, Rohypnol, and/or GHB). However, this study did not differentiate among various 'club' drugs and their use was not explicitly associated with rave attendance. Finally, in a large European investigation of the drug taking patterns of rave attendees, over 90% of ecstasy users reported the simultaneous use of at least one additional psychoactive substance during their most recent administration of the drug (Tossmann et al., 2001). However like other studies, this investigation did not delineate rave specific ecstasy use and polysubstance use patterns involving drugs other than ecstasy were not reported. The purpose of the present investigation was to better delineate the patterns of simultaneous polysubstance use that are characteristic of rave attendance by documenting amount, order, and type of all substances consumed on a single occasion by a sample of rave attendees from Montreal, Canada.

3.3 Methods

3.31. Procedure

Participants were recruited between November 2002 and September 2003 through advertisements posted at rave venues and on internet rave-related bulletin boards as well as by word of mouth from individuals already participating in the study. Subjects were eligible for inclusion if they had attended at least one rave in the preceding 6 months and resided in the greater metropolitan area of Montreal, Canada. All participants were assured that the information they provided would remain strictly confidential and were paid C$10 for their time. Interviews took approximately 30-40 minutes to complete and were conducted by two of the authors (SPB & IG). Prior to the beginning of the study each interviewer had completed training in structured interview techniques and each had experience in using the 'time-line follow back method' (Sobell & Sobell, 1996) of delineating patterns of substance use.

3.32. Structured Interview

The structured interview collected details about the participants' demographic characteristics as well as their 'Rave' attendance patterns including age of first attendance and an estimation of total number of events attended. In addition, detailed information was collected about drug and alcohol consumption at the most recently attended event using an interview format based on the time-line follow-back method (Sobell & Sobell, 1996). Participants were asked to think about the last event that they attended and

provide details about its date and location. They were then asked to recall all drugs consumed on that particular occasion (prior to, during, and after the event), including alcohol and tobacco. After spontaneously generating a list, participants were read a list of substances that they had not already mentioned and were asked if each substance was used at the time. The drugs included were alcohol, tobacco, cannabis, cocaine, amphetamine (speed, methamphetamine), MDMA (ecstasy), ephedrine, methylphenidate (Ritalin), amyl nitrate (poppers), GHB, ketamine (Special K), psilocybin (magic mushrooms), LSD, Heroin, benzodiazepines, PCP, inhalants, mescaline, morphine, opium, viagra, and 'any other drug not already mentioned' (please specify). After listing every drug consumed participants were asked to provide an ordered enumeration of their administration of all of the substances used on that occasion (excluding tobacco) as well as to provide details about the total amounts used of every substance. Additional details regarding the context of and reasons for specific patterns of drug administration were not routinely collected.

3.33. Test-Retest Reliability

In order to determine the reliability of participants' recollections of their rave-related substance use, a subset of the sample was contacted 24 to 72 hours following their initial interview and was asked to complete a second interview for the same event that they initially reported on. These participants were not randomly selected but rather represented the final 27 subjects

interviewed. Although each of these participants were informed that they may be re-contacted to provide additional information, they were not told that the purpose of the second interview would be to determine the reliability of their initial responses.

3.4 Results

3.41. Sample characteristics

A total of 186 (50% female) rave-attendees completed the interview. Participants' age ranged from 16 to 47 years (mean=23.5; sd=5.15; median=22; mode=22) and the majority were Caucasian (87.9%). Education levels were fairly high among this group with 87.6% having completed high school and 59.5% completing at least some post secondary education. 72.6% of the subjects identified themselves as heterosexual, 14.5 % homosexual and 12.9 % bisexual.

3.42. Rave Attendance

Subjects attended a rave for the first time on average at 18.9 (sd=4.6) years of age. The total number of raves attended varied between 1 and 400, with a mean of 48.6 events (sd=69.7), a median of 25 events and a mode of 50 events; 31.7% attended 50 events or more. 83.9% of the respondents reported using drugs or alcohol 'often' or 'always' when they go to raves.

3.43. Number of Substances Used at the Most Recently Attended Rave

Participants' rave substance use varied considerably, ranging from 0 to 7 different substances (excluding tobacco) with a mean of 2.5 (sd=1.2) different substances consumed. While only 2.7% of participants reported no substance use and 17.2 % reported the use of a solitary drug, approximately 80% reported polysubstance use.

3.44. Rave-Related Tobacco Use

Although 48.7% of participants identified themselves as regular daily smokers, 59.1% reported smoking tobacco at the most recent event attended. Concurrent tobacco use was reported in the majority of cases with every other type of drug reported (ranging from 61.5% of GHB users to 76.5% of cocaine users). However, because tobacco is typically considered to be a substance devoid of significant intoxicating properties (e.g. Perkins, 2002) and its use was typically continuous throughout an event, it was decided to exclude it from all subsequent analyses of poly-drug taking patterns.

3.45. Rave-Related Polysubstance Use

In order to begin to delineate the specific polydrug use patterns at the most recent rave event attended we calculated the percentage of respondents who had used each drug as well as the percentage of these users who reported simultaneous use of each other drug. Table 3.1 presents this data for all substances used by at least 5% of the sample. Additional analyses were performed to determine the order of initial administration of each substance, the proportion of users administering the drug in multiple sessions, the total number of substances concurrently used with each drug as well as the total average doses consumed (Table 3.2).

Cannabis was the most commonly used substance (n=120, 64.2%) at the most recent rave attended, and in 97.5% of the cases at least 1 additional psychoactive substance was also administered. Cannabis was co-administered by the majority of users of all other types of substances reported, ranging from 65.9% of amphetamine users to 76.9% of GHB users (Table 3.1). As shown in Table 2, although it was frequently first administered toward the middle of the drug taking sequence, in the majority of the cases (55%) it was reported to be used in multiple sessions interspersed with other substance use. The average cannabis user reported smoking 1.4 (s.d=1.2) grams over the course of the evening.

Alcohol was the next most frequently reported substance with 52.2% (n=97) of the sample reporting use. In 88.7% of these cases it was used with a minimum of one additional psychoactive substance, although the frequency of concurrent alcohol use varied considerably across substances ranging from 15.4% of GHB users to 76.5% of cocaine users (Table 3.1). Alcohol was typically consumed near or at the beginning of the drug taking sequence and in only 17 (17.6%) of the cases did its initial use follow other substance administration (Table 3.2).

Table 3.1: Patterns of substance use at the most recently attended rave.[a]

Drug	Any use (%)	Percentage of users reporting concurrent use of each substance							
		Cannabis	Alcohol	MDMA	Amphetamine	Cocaine	Ketamine	GHB	None[b]
Cannabis	64.9	XXX	55.0	52.5	48.3	10.8	9.2	8.3	2.5
Alcohol	52.2	68.0	XXX	43.3	36.1	13.4	9.3	2.1	11.3
MDMA	50.0	68.5	45.2	XXX	48.4	9.8	9.7	8.6	9.7
Amphetamine	47.8	65.9	39.3	50.6	XXX	5.7	14.6	12.4	11.2
Cocaine	9.1	76.5	76.5	52.9	29.4	XXX	23.5	11.8	0
Ketamine	8.6	68.8	56.3	50.0	81.3	25.0	XXX	18.8	0
GHB	7.0	76.9	15.4	69.2	86.4	15.4	23.1	XXX	0

[a]Data is reported for all substances used by a minimum of 5% of the total sample (n=186). The table present the percentage of respondents reporting any use of each substance, the percentage of users of each drug reporting concurrent use of each other substance.

[b]excluding tobacco

Table 3.2 : Order of administration, proportion of users administering substance in multiple sessions interspersed with other drug use, number of drugs co-administered and total dosage for each substance used by a minimum of 5% of participants.

Drug	Order of first administration	Multiple Sessions	Number of Drugs Co-administered[a]	Estimated Total Dosage
	Mean (sd)	%	Mean (sd)	Mean (sd)
Cannabis	2.0 (1.0)	55.0	2.0 (1.1)	1.4 (1.2) grams
Alcohol	1.3 (0.7)	22.7	1.9 (1.2)	6.4 (5.8) drinks
MDMA	2.5 (1.0)	9.9	2.0 (1.2)	1.1 (0.6) pills
Amphetamine	1.9 (0.8)	20.2	1.9 (1.2)	1.1 (0.4) pills
Cocaine	2.9 (1.1)	41.2	2.8 (1.0)	0.6 (0.9) grams
Ketamine	3.1 (1.4)	18.8	3.1 (1.4)	0.4 (0.2) grams
GHB	3.1 (1.6)	30.8	2.9 (0.9)	1.7 (1.0) uses

[a] excluding tobacco

MDMA and amphetamines were each used by approximately half of the sample, although 73.7% reported using at least one of these drugs. In close to 90% of the cases each of these drugs was used in a polydrug context (Table 3.1). The most frequent drugs used with MDMA were cannabis (68.5%), amphetamines (48.4%) and/or alcohol (45.2%), while amphetamines were most often used with cannabis (65.9%) and MDMA (50.6%). As Table 3.2 illustrates, on average both amphetamine and MDMA were used with approximately 2 additional substances. Moreover, for both drugs, users typically used a single dose in a single administration.

Cocaine (9.1%), Ketamine (8.6%) and GHB (7%) were each reported by fewer than 10% of the sample and in every case, each of these drugs was used in a polysubstance context (Table 3.1). Moreover, each of these drugs was typically consumed late in the drug taking sequence and in combination with approximately 3 other psychoactive substances (Table 3.2). The most frequently co-administered drugs with cocaine were alcohol (76.5%), cannabis (76.5%) and MDMA (52.9%). Ketamine was most often used with amphetamine (81.3%), cannabis (68.8%), alcohol (56.3%) and MDMA (50%), while for GHB, concurrent amphetamine (86.4%), cannabis (76.9 %) and/or MDMA (69.2 %) use were most frequently reported. It is interesting to note that a full 100% of GHB users reported the concurrent use of at least one stimulant drug (amphetamine, cocaine, ephedrine, methylphenidate and/or MDMA), while 93.7% of Ketamine users reported simultaneous stimulant use.

Substances reported by fewer than 5% of the sample and thus not included in Tables 1 and 2 were ephedrine (3.2%), psilocybic mushrooms (3.2%), LSD (2.7%) and methylphenidate (1.8%). In 100% of the cases each of these substances was used in conjunction with at least 1 other psychoactive substance. However, specific patterns of polydrug use involving these substances were not delineated due to the small number of respondents reporting their use.

3.46. Order of Drug Administration

In order to identify the specific temporal sequence of polydrug consumption, a series of Wilcoxon tests for related-samples were performed on each possible drug pairing, including all of the substances noted in Tables 3.1 and 3.2 . Because this resulted in 21 separate analyses, a family Bonferroni correction was used and the threshold for statistical significance was placed at p=0.002. Analyses revealed that when alcohol was used in drug combinations that included any of cannabis, MDMA, amphetamine or cocaine, its use reliably precedes the initiation of each other substance use (P's <.002). Moreover a similar trend was also evident for alcohol use preceding ketamine (P=.043) use, however a small sample size (9 cases) may have prevented this association from reaching the threshold for significance. Despite the high levels of drug mixing, there was only one other case where the relative order of drug administration was found to be reliable. When used in combinations that include MDMA, amphetamine use was found to reliably precede MDMA use (p<.001).

3.47. Relationship Between Rave Attendance and Drug Use

Using a Pearson's Correlation Coefficient, a significant positive relationship was identified between the total lifetime number of Rave events attended and the number of drugs used at the most recent event (r=.259, p<.001). In order to determine how the use of specific substances were related to level of rave attendance, a series of ANOVAs were performed with 'total

number of raves attended' as the dependent variable and with the independent variables being each drug reported by a minimum of 5% of respondents, while controlling for the possible effects of age, gender and sexual orientation by including them as covariates. (Table 3.3) Although no significant relationships were revealed between rave attendance and the use of alcohol, cannabis, amphetamine or MDMA, there were very strong associations between number of raves attended and the use of cocaine, ketamine, and GHB (Ps<.001).

Table 3 : Mean (S.D) number of raves attended by users of various substances and the relationship between substance use and level of rave attendance when controlling for various demographic variables N=186.

Drug	Number of raves attended [a]		F [b]
	Users	Nonusers	
Alcohol	51.1 (74.7)	46.1(61.8)	.82
Cannabis	46.6 (64.0)	53.3(77.2)	1.03
MDMA	46.1 (61.7)	51.3 (75.3)	.01
Amphetamine	60.6 (80.7)	37.8 (53.6)	1.6
Cocaine	107.8 (117.1)	42.9 (59.3)	19.7***
Ketamine	127.5 (111.7)	41.3 (58.4)	18.5***
GHB	132.8 (107.9)	42.3 (60.7)	17.8***

[a] Means (S.D) were calculated separately for individuals reporting use of a particular substance at the most recently attended rave (users) and those not reporting use of that substance at the last rave (nonusers).

[b] All analyses of variance were performed with gender, age, and sexual orientation as covariates; (df =1, 181).

*** P<.001

Table 3.4: Level of rave attendance predicts the probability of cocaine, GHB and/or ketamine administration at the most recently attended event using logistic regression.

Predictor Variable	Chi Squared χ^2	Wald Z	Odds ratio	95% Confidence Interval for Odds Ratio
Cocaine				
Raves attended	9.44**	13.33***	1.013	1.006 - 1.021
Age	1.18	0.92	0.939	0.826 - 1.068
Gender	4.19	4.60	0.221	0.055 - 0.883
Sexual Orientation	0.71	0.42	0.722	0.328 - 1.588
GHB				
Raves attended	12.81***	9.81**	1.010	1.004 - 1.016
Age	0.36	0.28	1.027	0.931 - 1.132
Gender	0.20	0.26	1.428	0.360 - 5.663
Sexual Orientation	0.12	0.12	1.116	0.501 - 2.695
Ketamine				
Raves attended	14.84***	9.08**	1.009	1.003 - 1.016
Age	0.26	0.05	0.989	0.897 - 1.092
Gender	0.00	0.21	1.342	0.386 - 4.666
Sexual Orientation	3.63	3.86	1.985	1.001 - 3.933

**P<.017
***P<.001

In order to further delineate the relationship between rave attendance and the use of cocaine, ketamine and/or GHB at the most recent rave attended, odds ratios were calculated using a binary logistic regression model. In each case number of raves attended, age, gender and sexual orientation were used as potential predictors of the outcome variable, use or non-use of the drug and both chi squared and Wald values were determined. Table 3.4 presents the results of these analyses. Because separate analyses were required for each substance, a family Bonferroni correction was used and the threshold for

statistical significance was placed at P=0.017. In each case, the number of raves attended remained the sole variable to reliably distinguish between those reporting use of the drug and those not. Moreover, odds ratios revealed that the probability of using each of these drugs at the most recent rave attended increased between approximately 9%-13% for every 10 raves attended (Table 3.4).

3.48. Test-Retest Reliability

The final 27 subjects (12 male, 15 female) interviewed were contacted by telephone 24 to 72 hours following their initial completion of the study and were again asked to recount the details of their drug taking for the same event they initially reported on. In 25 of the 27 cases (92.6%), participants reported the exact same series of substances during both interviews. Pearson's correlation coefficients were calculated to determine the consistency of reports for all drugs used by 5 or more subjects as well as for the doses reported, while Cohen's Kappa was used to determine the reliability of the ordinal drug taking sequence data. These data are presented in Table 3.5. Pearson's correlations revealed very high correlations for all drugs tested (ranging from .87 to 1.0) suggesting that participants were consistent in their reports of what drugs were used on the particular occasion as well as in the dosages reported. Moreover Cohen's Kappa values for drug order data generally indicated very good reliability with values ranging from .65 to 1.0.

Table 3.5: Test-retest reliability of participants' reports for substance use at the most recent rave attended (n=27).

Drug	N	Pearson's correlation: substance used	Pearson's correlation: reported dose	Cohen's Kappa: Order of administration
Alcohol	22	.88***	.98***	.65**
Cannabis	18	1.0***	.96***	.84***
MDMA	14	.93***	.87***	.89***
Amphetamine	8	.92***	1.0***	.81***
Cocaine	5	1.0***	1.0***	1.0***

** P=.001

*** P<.001.

3.5 Discussion

The present results are consistent with previous reports of high levels of drug mixing among rave attendees (e.g. Riley et al., 2001; Lenton et al., 1997) and suggest that simultaneous polysubstance use may be normative in this population. Approximately 80% of the present sample reported multiple substance administration at their most recently attended rave-event, and nearly 50% reported the concurrent use of three or more drugs. The use of multiple substances at raves is increasingly becoming a well-documented phenomenon, however to our knowledge the present investigation is the first to delineate the specific patterns of drug administration associated with rave attendance. Moreover, this study also presents evidence that participants can reliably recount details about the type, order and amount of all substances used on a specific occasion. While test-retest reliability data was only collected on a subset of participants (n=27), analyses revealed that individuals were highly concordant in their reports and despite the modest sample size, the information provided was found to be highly reliable (Table 3.5).

Cannabis, the most commonly used substance by the present sample, was used almost exclusively in a polydrug context. It was reported to be co-administered by the majority of users of all other substances and in most cases, was used over multiple sessions interspersed with other drug administration. Given its frequent administration with substances from various pharmacological classes as well as its pattern of continuous administration, it is

reasonable to assume that cannabis use is likely regarded as fairly benign activity among rave attendees. Although little is known about the effects of cannabis when it is co-administered with other substances, at least in the case of alcohol, cannabis has been demonstrated to produce additive intoxicating effects (e.g. Ramaekers et al., 2004). It should be noted however, that the solitary administration of even large doses of acute cannabis are generally not considered toxic (e.g. Grotenhermen, 2003) and to our knowledge there are no conclusive reports of acute cannabis use contributing to another drug's toxicity.

Alcohol, the second most frequently reported substance was normally used at or near the beginning of the drug taking sequence and did not usually continue following other substance administration. Because alcohol use typically preceded other drug administration it is possible that its use may have increased the probability of other substance use at least in some individuals. Alternatively alcohol use may occur exclusively in the early stages of the drug-taking sequence due to more pragmatic reasons. Alcohol's availability is often limited or prohibited at many rave venues and because its administration is a more conspicuous than most other forms of substance use, its consumption may be limited to the time immediately prior to the event. Alcohol co-administration with substances such as MDMA (Hernandez-Lopez et al., 2002), cocaine (McCance-Katz et al., 1998), and methylphenidate (Barrett & Pihl, 2002) has been reported to augment euphoric drug-effects and it is

possible that this may contribute to its propensity to be used concurrently with certain drugs. The practice of drug-alcohol co-administration has also generated considerable concern. Alcohol use with drugs such as cocaine (e.g. McCance-Katz et al., 1998) or methamphetamine (Mendelson et al., 1995) is thought to lead to increased toxicity and co-administration with central nervous system (CNS) depressants such as GHB may produce lethal effects (e.g. Smith et al., 2002). The present finding that alcohol is frequently administered prior to the use of drugs from various classes highlights the importance of continued research into the effects and consequences of alcohol-illicit drug co-administration.

Ecstasy and amphetamine also emerged as two of the most popular substances used by the sample, confirming previous reports that these are among the most commonly used drugs by Canadian rave attendees (Gross et al., 2001). While nearly three-quarters of the sample reported using at least one of these substances, approximately half of the users of each drug reported using both. Interestingly in cases where both drugs were used, amphetamine was found to reliably precede MDMA use, suggesting that order of administration may contribute to the positive effects that have been associated with the concurrent use of these drugs (Riley et al., 2001; Winstock et al., 2001). In most cases MDMA and/or amphetamine use were each limited to the administration of a single dose, a practice that presumably minimizes the probability of overdose. On the other hand, in the vast majority of cases

MDMA and amphetamine were used in a polysubstance context, which might increase the occurrence of adverse outcomes. Multiple substance use has been implicated in the majority of documented methamphetamine (see Mendelson et al., 1995) and MDMA (Schifano et al., 2003) related fatalities. However because these drugs seem to be routinely used in a polydrug context, the clinical significance of such findings remain unclear.

A minority of participants reported the use of cocaine, ketamine and/or GHB at the most recently attended rave. Each of these substances has been demonstrated to have toxic properties (e.g. Smith et al., 2002; Freese et al., 2002; McCance-Katz, 1998) and the consequences associated with their use in a polydrug context remain largely uninvestigated. Individuals that used any of these drugs administered more substances concurrently and had attended significantly more raves relative to other participants. These findings are consistent with previous research on rave attendees that found that the use of any cocaine, ketamine or GHB tended to occur relatively late in the course of "drug experimentation" and was most prominent among individuals that reported having extensive histories of drug use (Gross et al., 2001). Such results also raise the possibility that frequent rave attendance may lead to more dangerous drug taking practices and suggest that prevention efforts should be directed toward individuals already immersed in 'rave' subculture.

The present results should be interpreted in light of the following methodological limitations. First, because the participants were self-selected and the sample size was relatively modest, it is possible that the present results are not representative of population wide rave-related poly-substance use patterns. Although the rave attendees in the present sample represent individuals from a wide age rage (16-47 years) and level of rave experience (1-400) and the rates of polysubstance use reported were comparable to those obtained in different larger scale investigations using a variety of sampling techniques (e.g. Fendrich et al., 2003; Tossman et al., 2001; Winstock et al., 2001), only a true random sample of rave attendees would ensure the generalizability of these results. Second, because this study relied exclusively on retrospective recall, the accuracy of the information reported might be questioned. Previous research suggests that when appropriate interview methods are used that substance use self-report data can yield both reliable and valid results (e.g. Fals-Stewart et al., 2000; Sobell et al., 1996). In the present study a measure of test-retest reliability revealed that participants were highly consistent in their reports suggesting a high degree of accuracy. However, the validity of the reports were not verified using objective drug detection methods and it remains possible that in some cases that the extent of drug use may have been under reported (Fendrich et al., 2004). Finally, although the level and type of substance use on any particular occasion is likely related to numerous factors such as the availability of different substances, the presence or absence of drug using peers and the desire the achieve certain psychoactive effects (e.g.

Sloboda, 2002) the present investigation did not systematically address contextual and motivational factors surrounding rave-related polysubstance use and such issues should to be addressed in future investigations.

4. Study 1 Postscript and Abridging Statement to Study 2.

In study 1, specific patterns of simultaneous polysubstance use in rave attendees were delineated and it was found that concomitant use of multiple substances is a very common phenomenon in this population, that rave attendees appeared to be able to reliably recount numerous specific details about their patterns of multiple substances, and that alcohol was among the most frequently co-administered substances with various other drugs. Because most the analyses were selected to delineate overall patterns of rave-related drug use and did not specifically address how alcohol is used in combination with different abused substances, this paper provides only limited information about alcohol use in a polydrug context. When alcohol was used in most drug combinations, its initial use tended to precede the onset of other substance administration; however the significance of this finding is difficult to decipher due to the fact that there may be a limited availability of alcohol at many rave events and many are all-night parties that continue well past the time that alcohol can be legally sold. Moreover, although restricted alcohol availability might also contribute to the observation that alcohol administration did not appear to continue following the initiation of other substance use, these findings represent the overall drinking trends across the entire sample and it is possible that specific patterns of alcohol use may be associated with its co-administration with specific substances. In order to begin to test this hypothesis post-hoc analyses were performed to determine if patterns of alcohol-drug co-administration were related with the use of any particular

substance. Chi-squared analyses were used to determine if there were significant differences in the proportions of users and nonusers of each substance that continued to use alcohol following the onset of other substance use. Analyses revealed that among both cocaine and tobacco users that alcohol was significantly more likely to be used in multiple sessions interspersed with other substance use when it was used in combination with these drugs ($Ps<0.01$) and that this pattern of administration was not related to the administration of any other substances ($Ps>0.2$). While such findings suggest that alcohol administration patterns may be affected by the co-administration of certain substances the degree to which such findings may extend beyond a rave-specific context remains unknown.

In order to better delineate how alcohol and drugs are simultaneously co-administered, in study 2 we examined multiple substance use patterns in a sample of illicit-drug using college students. For each substance ever used, participants were asked to provide details of the order, amount and type of all substances taken using a specifically recalled event where the substance was used (most recent) as a point of reference. By examining simultaneous patterns across all substances ever used, we hoped to determine if patterns of alcohol (and other substance) administration were systematically associated with the co-administration of particular substances or classes of substances.

5. Study 2

Patterns of Simultaneous Polysubstance Use in Drug Using College Students

Sean P Barrett, Christine Darredeau, Robert O. Pihl

Department of Psychology, McGill University

5.1 Abstract

Simultaneous polysubstance use (SPU) has been reported to be a common phenomenon across different drug using populations, yet little is known about how various substances are used with one another. In the present study one hundred and forty-nine college students who reported illicit substance use completed structured interviews about their use of various substances. For each substance ever used, participants provided details about their most recent administration the drug including information about the type, order and amount of all substances co-administered during the session. Patterns of SPU are reported for all substances used by a minimum of 10% of the sample (alcohol, cannabis, tobacco, psilocybin, MDMA, cocaine, amphetamine, methylphenidate, LSD, ephedrine, ketamine, GHB and mescaline). Alcohol, tobacco and cannabis were frequently co-administered with each other as well as with all other substances and across all substance the majority of users reported using the substance in a SPU context during their most recent administration. When alcohol was used with other substances its initial administration tended to precede the use of all other drugs and when it was used with psychostimulant drugs (amphetamine, cocaine, or methylphenidate) it was found to be reliably used over multiple administrations interspersed with the psychostimulant drug and the quantities of alcohol ingested tended to exceed those consumed when it was used in the absence of other substances. When cannabis was used with alcohol or psilocybin its initial use tended to follow the administration of the other substance, however in all other cases its

pattern of use did not appear to be related to other substance(s) administered. Finally, in most cases tobacco use was reported to be increased relative to 'sober' smoking rates it was used in conjunction with other substances. Results suggests that many different substances appear to be routinely used in a SPU context and in some cases, that the pattern in which a particular substance is administered may largely depend on other substances co-administered.

5.2 Introduction

Substance users often use more than one psychoactive substance during the same session, a phenomenon known as simultaneous polysubstance use (SPU) (e.g. Martin et al., 1996a). Although SPU is believed to be a common practice (e.g. Earleywine & Newcomb, 1997) and has been documented across different drug using populations including alcoholics (Martin et al., 1996a; Staines et al., 2000), college students (Webb et al., 1997), rave attendees (e.g. Barrett et al., 2005b) and adolescents (Martin et al., 1993a, 1996b), most studies that have described trends in SPU have primarily focused on whether or not two or more target substances had been used together over a prescribed period of time (e.g. Leri et al., 2004, Martin et al., 1996a) and little is known about the specific patterns of co-administration or about how such patterns might vary across different substances.

Because many abused substances may be frequently used in a SPU context, delineating the patterns of concurrent multiple substance use may have important implications for understanding the abuse potential of such drugs. The concomitant use of some substances might result in significant pharmacological interactions that alter the subjective and/or behavioural effects of the drug (e.g. Leri et al., 2003; Herndez-Lopez et al., 2002) and that might affect its abuse potential. Moreover because experimental evidence suggests that the way that certain commonly co-administered drugs interact may depend on factors such as their relative order (s) administration and doses

(e.g. Perez-Reyes et al., 1992; Perez-Reyes, 1994), it is possible that polydrug users preferentially co-administer some substances in a particular orders and quantities in order to achieve desirable results.

We have recently documented the patterns of SPU in a sample of 'rave' attendees using a standardized structured interviews technique where participants recounted details of about the order and amounts of all substances administered at a specific (the most recently attended) rave-event. Results revealed that for every drug used by the sample (cannabis, tobacco, alcohol, MDMA, amphetamine, cocaine, ketamine, GHB, ephedrine, psilocybic mushrooms, LSD and methylphenidate) the majority of users administered the substance in a SPU context; that participants were to able to reliably recall precise details of regarding the order, amount and type of all substances administered and that certain substances appeared to follow identifiable patterns of co-administration (Barrett et al., 2005b). However because rave-related substance use patterns may be context specific (e.g. Tossmann et al., 2002), such findings might not extent to other drug using populations. In the present study, we used a similar method to examine the substance administration patterns in a sample of illicit drug using college students. For each substance ever used, participants were asked to provide details of the order, amount and type of all substances taken using the most recent specifically recalled administration of the substance as a point of reference.

5.3 Methods

5.31. *Procedure*

Participants were 149 individuals recruited from the McGill University student population between April 2003 and August 2004 through advertisements posted on campus, on an Internet university classified ads site, as well as from a pool of volunteers that had expressed interest in participating in research in McGill's Department of Psychology. Participants were included in the study if they used at least two substances in their lifetime, including alcohol but not tobacco, and were assured that the information provided would remain strictly confidential. A subset of the sample (N= 48) was recruited on the basis of their previous recreational/non-prescribed use of the prescription drug methylphenidate or served as matched controls for these subjects (N=38). Additional details about these participants have been reported elsewhere (Barrett et al. 2005a).

5.32. Structured Interview

The structured interview used a retrospective self-report standardized measure to collect details about patterns of simultaneous substance use. Participants were asked to spontaneously list every substance they had used to get 'high, drunk, stoned or buzzed' in their lifetime. Once finished, the interviewer read from a standard list of substances in order to stimulate participant recall of any use not previously mentioned. The standard drugs on

the list were alcohol, cannabis, LSD, psilocybin (magic mushrooms), cocaine, mescaline, amphetamine (speed, methamphetamine), methylphenidate (Ritalin), Phencyclidine (PCP) , ketamine, GHB, MDMA (ecstasy), heroin, ephedrine, Adderall, Dexedrine, and 'any other drug not already mentioned' (please specify). Participants were asked to provide several details about each drug they had used, including their age of first use, and number of uses during the preceding 30 days. In addition for each substance, participants were asked to indicate if they had ever co-administered other substances during a session it had been used and if so to list all of the substances ever been mixed with the drug. The participants were then asked to think about the last time they had used each substance and to recall several specific details about this occasion including the location and approximate date. These details were elicited in order to anchor recollections to a specific occasion. In cases where participants were not certain of the details of the most recent event they were asked to recall the most recent specific occasion that could be recalled to be used as a reference point. For each substance ever used participants provided an ordered enumeration of all substances used during the recalled session (excluding tobacco) as well as to provide an estimate of the total amount of each substance used using standardised units. If tobacco had also been used during the session, the participant was asked to indicate whether they smoked more, less or about the same as they usually do when not using any other substances. In addition for alcohol, participants were also asked if they had ever used it by itself; that is without any other substances excluding tobacco. If

they reported solitary alcohol use they were asked to recall a specific representative occasion when this took place and to provide an estimate of the amount of alcohol that was consumed. If tobacco was also used during this occasion they were again asked whether there were any changes in their normal (sober) smoking patterns.

5.4 Results

5.41. Sample Characteristics

A total of 149 (58.7% female) polysubstance users completed the interview. Participants' mean age was 21.7 (sd=3.5) and the majority were Caucasian (78.5%). On average participants reported experience with 6.7 (sd=3.42; range=2-17; median=6; mode=3) different substances including tobacco and all participants reported using alcohol and cannabis.

Table 5.1: Substance use characteristics of the sample

DRUG	Lifetime use N (%)	Age of first use Mean(SD)	Use in past 30 days (%)	Lifetime alcohol co-use (%)	Lifetime cannabis co-use (%)
Alcohol	149 (100)	14.1 (2.4)	97.2	XXX	94.5
Cannabis	149 (100)	15.4 (2.2)	71.9	94.5	XXX
Tobacco	136 (91.3)	14.7 (2.7)	41.5[b]	NA	NA
Psilocybin	97 (65.1)	17.0 (2.2)	18.6	66.0	82.5
Ecstasy	75 (50.3)	18.1 (2.7)	13.2	67.1	68.4
Cocaine	64 (43.0)	18.8 (2.1)	39.3	91.9	70.0
Amphetamine	54 (36.2)	18.3 (3.1)	16.3	61.4	45.6
LSD	44 (29.5)	16.3 (2.8)	0.0	59.2	65.3
Methylphenidate[a]	42 (25.1)	18.5 (3.6)	28.6	64.3	52.3
Ephedrine	27 (18.1)	19.6 (3.0)	20.8	65.2	50.0
Ketamine	18 (12.1)	18.7 (2.2)	16.7	44.4	61.6
GHB	15 (10.1)	20.3 (4.2)	6.7	60.0	33.3
Mescaline	15 (10.1)	18.5 (2.4)	20.0	53.7	60.0

[a] Methylphenidate users were only included if they reported recreational use of the drug.
[b] Represents only regular daily tobacco use. NA=Data not available

Table 5.1 presents the proportion of participants reporting lifetime use each substance used by a minimum of 10% of the sample (alcohol, cannabis, psilocibin, MDMA, cocaine, methylphenidate, amphetamine, LSD, ephedrine, ketamine, GHB and mescaline), the age of its first use and the proportion of

participants using each substance during the 30 day period preceding the interview as well as the portion of the participants reporting lifetime co-administration with alcohol and cannabis (the two substances used by all of the participants) . Substances reported by fewer than 10% of the sample are not included in Table 5.1 or in any of the subsequent analyses. These were morphine (9.4%), benzodiazepines (8.1%), Dexedrine (8.1%), Adderall (6.0%), PCP(6.0%), heroin (4.7%), divine sage (4.7%), Percocet (4.7%), codeine (3.4%), dextromethorphan (DXM) (3.4%), nitrous oxide (3.4%), inhalants (3.4%), steroids (0.7%), and N,N-dimethyltryptamine (DMT) (0.7%).

5.42. Patterns of simultaneous polysubstance administration

In order to delineate patterns of simultaneous polysubstance use, for each drug the proportion of users that co-administered each other substance during the most recent recalled administration of the drug was calculated. These data are presented in Table 2. Tobacco was the most commonly co-administered drug with all substances with the exceptions of cocaine and mescaline where it was the second most frequently concomitantly used substance. Moreover in all cases tobacco, alcohol, and cannabis were the three most commonly concomitantly used substances, with the majority of users of each drug co-administering at least one of these substances during their most recent recalled administration.

Table 5.2: Simultaneous polysubstance use during most recent recalled administration of each drug

Substance	Alcohol (%)	Cannabis (%)	Tobacco (%)	Alcohol, tobacco and /or cannabis (%)	Other drug(s) (%)	None (%)
Alcohol	XXX	28.2	46.9	55.1	5.3	44.9
Cannabis	37.6	XXX	47.9	65.7	2.0	32.9
Psilocybin	41.2	59.8	61.9	85.6	5.6	9.3
Ecstasy	42.7	27.6	64.0	81.3	20.0	16.0
Cocaine	79.7	40.0	77.0	95.3	7.8	4.7
Amphetamine	41.5	44.9	66.7	83.3	20.4	13.0
LSD	25.0	40.5	69.8	78.6	18.1	13.6
Methylphenidate	35.7	28.2	56.8	66.7	7.1	28.2
Ephedrine	40.7	26.1	65.2	81.5	11.1	18.5
Ketamine	38.3	33.3	83.3	88.9	33.3	5.6
GHB	40.0	26.7	46.7	73.3	26.7	20.0
Mescaline	46.6	60.0	53.3	80.0	20.0	20.0

5.43. Patterns of polysubstance use

Additional analyses were performed to determine if patterns of alcohol, cannabis or tobacco administration were systematically related to their use with other drugs. For each substance analyses were conducted for all cases where there were a minimum of 10 reports of the drugs being concomitantly administered during the most recent recalled event.

5.431 Alcohol

In order to identify the temporal sequence of alcohol-drug administration during the most recent recalled administration of each substance, a series of Chi-squared tests were performed to determine if there

was a systematic order of initial administration as well as to determine if alcohol was systematically used in multiple sessions interspersed with drug use. The results from these analyses are presented in Table 5.3. Analyses revealed that across most substances co-administered, that alcohol use typically preceded the use of each other substance, an effect that was statistically reliable for combinations involving cannabis, psilocybin, ecstasy, cocaine, methylphenidate, methamphetamine and LSD. Moreover, when alcohol was used in combinations that included cocaine, methylphenidate or amphetamine its use was found to reliably continue following the administration of the drug and to be interspersed with the substance over repeated administrations (Table 5.3).

Table 5.3: Sequence and pattern of alcohol administration in a SPU context

Drugs co-administered with alcohol (Number of reports)	Was alcohol used before the start of other drug use (%)	Chi-Square	Were alcohol and drug use intermingled? (%)	Chi-Square
Cannabis (55)	80.0	18.00**	45.5	0.36
Psilocybin (38)	72.5	8.10**	57.1	0.71
Ecstasy (30)	75.9	7.76**	31.8	2.91
Cocaine (49)	89.8	31.0**	79.1	14.54**
Amphetamine (20)	85.7	10.71**	73.7	4.26*
LSD (11)	81.8	4.45*	50.0	0.00
Methylphenidate (15)	93.3	9.31**	84.6	6.23*
Ephedrine (11)	60.0	0.40	66.7	1.00

** P<0.01; *P<0.05

Paired samples t-tests where used to determine if the amounts of alcohol reported to be ingested differed when it was used in a polydrug context relative to when it is used in the absence of other substances (excluding

tobacco). Table 5.4 presents the results of these analyses. Participants reported consuming significantly more drinks when alcohol was used in conjunction with either cocaine ($p<0.01$) or methylphenidate ($p<0.05$) relative to when they used alcohol in the absence of other substances (excluding tobacco) and there were also a nonsignificant trends toward an increased alcohol consumption when it was used in combinations with either amphetamine or ephedrine ($Ps \leq 0.1$).

Table 5.4: Amounts alcohol reported to be consumed when co-administered with other substance and during solitary[a] administration

Substance co-administered (Number of reports)	Total number of drinks consumed - Mean (SD)		T-test
	Alcohol Mixed	Alcohol Alone[a]	
Cannabis (55)	5.7 (4.2)	5.2 (3.5)	0.81
Psilocybin (38)	6.4 (4.2)	5.4 (2.8)	1.35
Ecstasy (30)	5.5 (4.5)	5.0 (3.3)	0.39
Cocaine (50)	7.8 (3.7)	5.3 (3.1)	3.94**
Amphetamine (20)	7.5 (3.5)	5.7 (3.4)	1.65
LSD (11)	5.1 (4.0)	3.7 (4.3)	0.72
Methylphenidate (14)	8.3 (5.0)	6.2 (3.6)	2.34*
Ephedrine (11)	8.0 (3.6)	6.9 (3.1)	1.94

[a] alcohol used in the absence of all other substances except tobacco
** P<0.01; *P<0.05

Because alcohol was often co-administered with more than one substance at a time post-hoc analyses were preformed to determine if the amounts of alcohol consumed when it was combined with either cocaine or methylphenidate significantly differed in the presence and absence of additional substances. Independent samples t-tests were used to compare the relative differences in alcohol drinks reported (co-administered – alone) between those that used additional substances (excluding tobacco) and those

that did not, as well as between those using tobacco and those not. There were no significant differences between the relative increase in amount of alcohol reported in cocaine users that administrated additional substances (other than tobacco) (N=22; mean=+ 1.6 drinks; SD=4.5) vs. that did those not (N=27; mean=+3.3 drinks; SD=4.5) [t (47) = -1.33; p=0.19]; or among methylphenidate users using additional substances (N=7; mean=+3.1 drinks; SD=3.0) vs. those not (N=7; mean= +1.2 drinks; SD=3.8) [t (12) = 1.06; p=0.31]. Moreover there were also no significant differences among cocaine users that used tobacco (N= 40; mean= +2.6 drinks; SD= 4.1) vs. those who did not (N=9; mean = + 1.9 drinks; SD=5.8) [t (47)=0.43; p=0.67] or among methylphenidate users that concurrently used tobacco (N=11; mean = +2.7 drinks; SD=3.4) vs. those who did not (N=3; mean= +0.2 drinks; SD= 3.7) [t(12)=1.14; p=0.28]. However it should be noted that these latter findings should be interpreted with caution given the high levels of variance and relatively low number of non-smokers.

5.432 Cannabis

Table 5.5 provides details of patterns of cannabis administration when it was used in a polydrug context. When cannabis was used with either alcohol or psilocybin, its initial use tended to follow the initial use of these substances, however sequence of cannabis use was not systematically related to the use of any other substance. Moreover in no cases was cannabis use found to be used over multiple sessions interspersed with other drug use and when it was used

with psilocybin there was in fact a significant tendency for it not to be used in this way. Because participants did not routinely provide standardized estimates of the amounts of cannabis administered in the absence of other substances it was not possible to examine possible changes in amounts administered when cannabis is used in conjunction with other substances.

Table 5.5: Sequence and pattern of cannabis use SPU context

Drug co-administered with cannabis (Number of reports)	Was cannabis used prior to other drug use (%)	Chi-Square	Were cannabis and drug use intermingled? (%)	Chi-Square
Alcohol (36)	33.3	4.00*	45.7	0.26
Psilocybin (55)	32.7	6.56*	34.0	5.12*
Ecstasy (32)	37.5	2.00	41.7	0.67
Cocaine (21)	42.9	0.43	37.5	1.00
Amphetamine (21)	33.3	2.0	33.3	2.00
LSD (17)	35.6	1.47	38.5	0.69
Methylphenidate (11)	41.7	0.33	30.0	1.60

** P<0.01; *P<0.05

5.433 Tobacco

Substance-related tobacco smoking data were coded as follows: decreased smoking relative to normal sober smoking patterns =-1; no change in relative smoking patterns = 0; and relative increased tobacco smoking =1. For each substance one-samples t-tests were performed to determine if there were associated changes in tobacco smoking patterns by testing the null hypothesis that there would be no change in smoking desire (mean=0). The results from these analyses are presented in Table 5.6. Increased tobacco smoking was associated with the administration of alcohol, cannabis, psilocybin, ecstasy, cocaine, amphetamine, LSD and methylphenidate. In order to determine the

specificity of the reported increases a series of independent samples test were performed to compare the change smoking patterns associated with each drug when the substance was used with multiple substance relative to when it was only co-administered with tobacco. Results indicated that when used with cannabis that there was a significantly greater relative increase in tobacco smoking when multiple substances were used compared to when only cannabis and tobacco were used together [t (68) = 2.78; P <0.01], suggesting that the overall reported increase in tobacco smoking associated with the most recent cannabis use may not be specific to an effect of cannabis. In contrast, for all other substances associated with increased tobacco administration there were no differences in the rates of smoking when comparing co-administering multiple substances relative to those only using the drug with tobacco (Ps>0.2).

Table 5.6 Changes in tobacco smoking in a SPU context

Drug co-administered with tobacco (Number of reports)	Changes in smoking patterns relative to normal 'sober' baseline			T-test
	Decrease (%)	No change (%)	Increase (%)	
Alcohol (69)	5.9	23.5	70.6	9.00***
Cannabis (70)	8.6	40.0	51.4	5.50***
Psilocybin (60)	15.0	15.0	70.0	5.71***
Ecstasy (48)	10.4	6.3	83.3	7.85***
Cocaine (47)	2.1	10.6	87.2	14.02***
Amphetamine (32)	6.3	9.4	84.4	8.00***
LSD (30)	16.7	13.3	70.0	3.76**
Methylphenidate (25)	16.0	28.0	56.0	2.62*
Ephedrine (15)	20.0	40.0	40.0	1.00
Ketamine (15)	33.3	20.0	46.7	0.58

***P<0.001; **P<0.01; *P<0.05

Discussion

The present results suggest that SPU is a very common phenomenon among drug-using college students. The majority of users of every substance investigated reported using multiple substances during their most recent recalled administration of the drug, with tobacco, alcohol, and cannabis being frequently mixed with each other as well as with all other substances. These findings are consistent with previous reports that many drugs are often used in a polydrug context (e.g. Leri et al., 2004; Martin et al., 1996a; Barrett et al., 2005), and suggest that patterns SPU should be considered when examining the addictive potential of different substances.

Tobacco was widely concomitantly used with all other drugs and in most cases substance administration was associated with overall increased levels of smoking. Although data regarding the timing of tobacco administration was not collected, smokers are thought to generally administer tobacco over multiple sessions (e.g. Batel et al., 1995) and given their reported high levels of tobacco use it is likely that participants smoked throughout the course of their substance administration sessions. Despite the high rates of simultaneous tobacco smoking with various abused substances, very little is known about how tobacco interacts with most other drugs. Nicotine, the main addictive alkaloid in tobacco (e.g. Domino, 1998), is a psychostimulant and like other psychostimulants it is believed to exert its reinforcing central affects through promoting midbrain DA neurotransmission (e.g. Pontieri et al., 1996).

Although nicotine's DA-related effects are believed to be relatively weak relative those produced by either cocaine or amphetamine (e.g. Tsukada et al., 2002) nicotine may facilitate DAergic response to other reinforcers (Rice & Craig, 2004; Zhang & Sulzer, 2004) and it is possible that its propensity to be used with certain substances may relate to this effect. While identification of the mechanisms responsible for the increased levels of smoking reported when tobacco is used in a SPU context remains a matter of conjecture, the high rates of simultaneous tobacco use reported in this study highlight the importance of considering possible effects of concomitant nicotine when studying the addictive properties of different drugs.

Consistent with previous reports, alcohol was also among the most commonly co-administered substances with a variety of drugs (e.g. Martin et al., 1996; Barrett et al., 2005). When alcohol was used in a polysubstance context its initial use tended to precede the onset of most other substances, raising the possibility that alcohol administration increases the probability of other substance use. A similar tendency for alcohol intake to precede other substance administration has also been recently reported among rave attendees (Barrett et al., 2005) indicating that this may be a common phenomenon across different drug using populations. The propensity for alcohol to be initially administered prior to other substances may be related to its effects on the pharmacokinetic properties of other substances. Evidence suggests that administering cocaine (e.g. Cami et al., 1998), d-amphetamine (Perez-Reyes et

al., 1992) and MDMA (Hernandez-Lopez et al., 2002) following alcohol pre-treatment may lead to increased plasma concentrations of these substances and that at least in the case of cocaine that this effect does not appear to occur when drug use precedes alcohol ingestion (e.g. Perez-Reyes, 1994). It is also possible some substances may be administered following alcohol in order to achieve a specific neuropsychopharmacological effect. During the ascending limb of the blood alcohol concentration curve when blood alcohol concentration are rising, alcohol's subjective effects are thought to be stimulant-like (e.g. Newlin & Thomson, 1990; King et al., 2002) and to be associated with increased DA neurotransmission and these DAergic effects are thought to promote alcohol ingestion (e.g. Weiss et al., 1994). It is thus tempting to speculate that certain drugs may be co-administered with alcohol due to their ability to augment alcohol-related DA neurotransmission. This notion is appears consistent with findings that when alcohol was used in combinations that included psychostimulant drugs known to increase DA neurotransmission such as cocaine (e.g. Wise, 1996), amphetamine (Drevets et al., 2001) and methylphenidate (Volkow et al.1995), it was reliably administered over several sessions interspersed with stimulant drug use and the number of alcohol drinks reported tended to exceed doses normally consumed in the absence of these drugs.

In addition to tobacco and alcohol, cannabis was also identified as a substance that is frequently co-administered with various drugs. However

unlike these other drugs its pattern of use did not appear to be systematically related to the use of most other substances. While the initiation of cannabis use was found to reliably follow alcohol and psilocybin use when it was co-administered with these substances, the order of cannabis administration did not appear to be systematically related to any other substance and in no case was cannabis use found to be reliably used over multiple sessions interspersed with other substance use. Nevertheless given the high prevalence of cannabis co-administration with various other substances the mechanisms and motives associated with its propensity to concomitant used with various substances clearly warrants further attention.

The present findings should be interpreted in light of the following methodological considerations. First because the sample size was modest, was limited to college students and the participants were self-selected these findings may not generalise to all college-student drug users. While the present study included drug users with variable levels of experience with different substances, further research is required to delineate the SPU patterns of more narrowly defined drug using populations. However it is important to note that irrespective of the sampling method used or the population targeted, achieving a truly representative sample illicit drug users would likely not be feasible. Second, because this study relied exclusively on retrospective recall, the accuracy of the information reported might be questioned. Previous research suggests that when appropriate interview methods are used that substance use

self-report data can yield both reliable and valid results (e.g. Fals-Stewart et al., 2000; Sobell et al., 1996). Because in the present study participants were required to only report on specific events that could be vividly recalled a relatively high degree of accuracy would be expected (Sobell et al., 1996). However, the validity of these reports were not verified using objective drug detection methods and it remains possible that in some cases that the extent of SPU use may have been under reported (Fendrich et al., 2004). Finally, although the level and type of substance use on any particular occasion is likely related to numerous factors such as the availability of different substances, the presence or absence of drug using peers and the desire the achieve certain psychoactive effects (e.g. Sloboda, 2002) the present investigation did not systematically address contextual and motivational factors surrounding specific patterns of polysubstance use and such issues should to be addressed in future investigations.

6. Abridging Statement to Study 3

In study 2 alcohol was found to be widely co-administered with a variety of substances and when it was used in combination with the psychostimulant drugs cocaine, methylphenidate or amphetamine its use tended to follow a systematic pattern characterized by 1) alcohol being used first; 2) subsequent alcohol ingestion being intermingled with psychostimulant use and 3) alcohol dose escalation. However, because tobacco was frequently co-administered in each of these combinations as well as with alcohol alone it was not possible to determine the extent to which tobacco use affects alcohol administration patterns. In study 3 the effects of nicotine on alcohol self-administration are directly assessed using a double-blind placebo control paradigm. Because nicotine is believed to exert similar neuropharmacological effects as other psychostimulants on DA neurotransmission (e.g. Pontieri et al., 1996) and alcohol does not appear to significantly alter nicotine's pharmacokinetics (Collins et al., 1988; Benowitz et al., 1986), delineating nicotine's effect on alcohol administration may help distinguish between pharmacodynamic and pharmacokinetic mechanisms associated with the reported increased alcohol administration with other psychostimulant drugs.

7. Nicotine increases alcohol self-administration in non-dependent male smokers

Sean P. Barrett[1], Matthew Tichauer[1], Marco Leyton[2], Robert O. Pihl[1,2]

Departments of Psychology[1] and Psychiatry[2] McGill University, Montreal Canada

7.1 Abstract

Background: Alcohol and tobacco are commonly co-administered, yet little is known about the effects of acute nicotine administration on alcohol consumption in humans. This study sought to determine how nicotine delivered by tobacco smoke influences alcohol intake in humans using a double-blind placebo controlled repeated measures design. *Methods:* During two randomized 120-minute sessions 15 male occasional smokers smoked 4 nicotine-containing or 4 denicotinized cigarettes at 30-minute intervals. Throughout the session, subjects could earn units of their preferred alcoholic beverage and glasses of water using a progressive-ratio (PR) task. *Results:* Wilcoxon signed-rank tests indicated that nicotine increased alcohol self-administration in a significant proportion of participants ($P \leq 0.03$) without affecting water consumption ($P \geq 0.16$). A two-way ANOVA supported this observation further, and, compared to denicotinized cigarettes, the nicotine-containing cigarettes increased PR breakpoints for alcohol but not water, as reflected by a Cigarette x Beverage interaction ($P \leq 0.055$). *Conclusions:* The present data suggest that acute nicotine administration increases alcohol consumption in at least a subset of smokers.

Key Words: alcohol, nicotine, addiction, self-administration, polysubstance use, progressive ratio

7.2. Introduction

The two most commonly abused substances in the general population, alcohol and nicotine, are frequently co-administered (e.g., Batel et al., 1995). The prevalence of tobacco smoking in alcoholics is thought to be as high as 90%, compared to less than 30% in the general population (e.g. Sobell et al., 1990; Romberger and Grant, 2004). Similarly, smokers are 50% more likely to drink regularly than adult non-smokers (Kozlowski and Ferrence, 1990). Some evidence suggests that these associations reflect an ability of ethanol and nicotine administration to increase motivation to obtain the other substance. In smokers, acute alcohol administration is consistently reported to increase cigarette self-administration (Griffiths et al., 1976; Mello et al., 1980; Keenan et al., 1990). In comparison, the converse association is less well understood. There are several reports that, in rodents, chronic or repeated nicotine administration increases alcohol consumption (Smith et al., 1999; Le et al., 2000; Clark et al., 2001; Soderpalm et al., 2000; Le et al., 2003), but this effect has not been uniformly replicated, and decreased alcohol self-administration has also been reported (Sharpe and Samson, 2002). Similarly, acute nicotine administration has been reported to increase (Gauvin et al., 1993), decrease (Nadal et al., 1998), and have no effect on alcohol intake (Nadal and Sampson, 1999). Such inconsistent findings may be related to differences in doses, administration regimens, or rodent strains (Le at al., 2002). The contribution of these factors to the co-administration of nicotine and alcohol in humans

remains unknown; to our knowledge, the effect of nicotine on alcohol self-administration in humans has yet to be determined. In a previous investigation acute cigarette smoking was found to increase alcohol related responding in male social drinkers (Perkins et al., 2000). However because this study did not have a placebo smoking condition it was not possible to determine the extent to which the findings resulted from a pharmacological effect of nicotine.

In the present study, we sought to determine how nicotine delivered by tobacco smoke influences alcohol administration in humans using a double-blind placebo controlled repeated measures procedure, in which cigarettes made of nicotine-containing or denicotinized tobacco were smoked throughout the course of a drinking session. Since nicotine withdrawal may affect alcohol craving and consumption in dependent smokers (Palfai et al., 2000; see also Cooney et al., 2003; Colby et al., 2004), the present protocol examined non-dependent occasional smokers to avoid this potential confound.

7.3. Methods

7.31 Participants

Fifteen non-dependent male 'occasional' smokers (80% Caucasian) between the ages of 18 and 30 (mean=22.3 ± 1.8) were recruited from the community through advertisements placed in local community newspapers and on university websites. All were medically healthy, free from current or previous mental illness including past or present substance use disorders (including nicotine dependence) as determined by a semi-structured clinical interview using DSM-IV criteria (First et al., 1995), and all scored a 0 on the Fagerström test for nicotine dependence (Heatherton, 1991). None reported the use of illegal drugs in the 30 days prior to the study, none were daily users of tobacco and none had a history of social, occupational or legal problems involving alcohol as determined by the Michigan Alcoholism Screening test (Pokorny et al., 1972). All had reached the minimum age to legally consume alcohol and tobacco in Quebec Canada and all reported having smoked a minimum of four cigarettes throughout the course of a drinking session on at least one occasion during the preceding year without experiencing any adverse consequences. On average participants reported consuming cigarettes on 2.7 ± 1.6 days and alcohol on 2.3±0.8 days per week. Average daily consumption on days when the substance was used was 5.4 ± 1.6 cigarettes per day and 5.9 ±2.1 drinks per day. Participants were informed that the study involved

smoking two different brands of tobacco but not that one of the sessions used denicotinized cigarettes. Following a description of the study, all participants provided written informed consent. The study was conducted in accordance with the Declaration of Helsinki and was approved by a McGill University Research Ethics Committee.

7.32 Cigarettes

Prior to the study participants were asked to identify the brand (s) of cigarettes that they smoked in order to ensure their unfamiliarity with the specific brands of tobacco used during the testing sessions. Participants were informed that on each test day that they would be required to smoke 4 cigarettes over a two-hour period and that on each test day that a different brand of tobacco would be used. All cigarettes contained 65 grams of tobacco, and were prepared to appear identical. The 'denicotinized' cigarettes were prepared using *Quest 3* tobacco (Vector Tobacco Inc, USA), and provided maximum nicotine yield of 0.05 mg and a tar yield of 10 mg. The 'nicotine' containing cigarettes were prepared using *Player's Light* tobacco (Imperial Tobacco Limited, Montreal Canada) and they provided nicotine and tar yields of 1.2 mg and 12 mg, respectively. This tobacco was selected for its relatively high nicotine to tar ratio and its relatively similar average tar yields to the denicotinized tobacco.

7.33 Alcoholic Beverages

Prior to the study sessions, each participant identified a preferred alcoholic beverage. The beverage could consist of any 80-proof liquor with a non-alcoholic mixer; the same beverage was to be consumed on both days. Choice of beverage was restricted to 80-proof liquors due to the high variability in the alcohol contents of commercially available brands of beer, wines and coolers. Participants were informed that on each test day they would be required to consume a minimum of one standard drink containing 12 grams of 80-proof alcohol (38 ml) and that the maximum dose of alcohol that could be consumed on any day was 72 grams or the equivalent of 6-full standard drinks.

7.34 Subjective State

Participants were administered visual analogue scales (VAS) at baseline and immediately following the completion of each cigarette on each test day. Items were rated on a ten cm line labelled with the integers 1-10 and anchored with the words "least" and "most". Items included in the VAS were 'high', 'stimulated', 'energetic', 'anxious', 'sedated', 'intoxicated', 'want alcohol', 'like cigarette', 'crave cigarette', and 'crave alcohol'. Similar scales have been widely used to collect information about subjective drug effects in humans (e.g. Fishman and Foltin, 1991) and this

method of data collection has been demonstrated to have acceptable psychometric properties (Bond and Lader, 1974).

7.35 Design

The research protocol was comprised of two test sessions. Each was conducted between 12pm and 4 pm in the afternoon, was a minimum of three and a maximum of fourteen days apart, was double blind, and was given in counterbalanced randomized order. In one condition subjects were required to smoke 4 'nicotine' cigarettes and in the second condition 4 'placebo' cigarettes were smoked. In both conditions, cigarettes were smoked at 30-minute intervals throughout the first 90 minutes of the 120-minute drinking session (t=0 min, 30 min, 60 min, and 90 min). All participants were tested on separate days.

Participants arrived for each testing session having abstained from cigarettes for a minimum of 12 hours, alcohol for a minimum of 24 hours and food and caffeine for a minimum of 4 hours (caffeine-free fluid intake was not restricted prior to the study). At this time they provided a breath alcohol sample using an alco-sensor III intoximeter (Thomas Security, Montreal, Canada) and a reading of .000 grams of alcohol per 210 liters of breath was required to confirm abstinence. Abstinence from tobacco was confirmed with a breath carbon monoxide analyzer (Vitalograph Breath CO, Lenexa, KS), using a maximum cutoff of 5 parts per million.

A timeline outlining the sequence of procedures is presented in Table 7.1. After completing baseline measures participants were comfortably seated in a chair in front of a glass containing 100 ml of water, a glass containing their preferred alcoholic beverage (containing 38ml of 80-proof alcohol and 100ml of mix) and a computer on a large table. They were told that after smoking their first cigarette of the day that they would receive one 'free' alcoholic drink but that all subsequent drinks of either type would have to be 'earned' using a computerized task (described below). Participants examined both of the drinks and were given instructions on how each could be earned. They were then told to smoke their initial cigarette. For each cigarette consumed they were instructed to inhale the smoke as well as to complete the cigarette to the filter. The pace and duration of the 'puffs' however was self-determined by the participant. Following the completion of their first cigarette participants were required to complete the VAS and then consume their 'free' alcoholic beverage within 10 minutes. The requirement for participants to administer this 'free' dose of alcohol was included in the protocol to normalize drinking in the laboratory, to ensure that alcohol was consumed on both test days and to enable comparisons with other studies examining alcohol self-administration in humans following a pharmacological manipulation (Modell et al., 1993; Perkins et al., 2000; Enggasser and de Wit, 2001; Petrakis et al., 2002; Leyton et al., 2004).

Immediately after consuming the 'free' dose of alcohol, participants could begin using a computerized progressive ratio (PR) task to earn up to 10 mixed alcoholic drinks, each containing 6 grams (19ml) of alcohol and 50 ml of mix, and up to 10 100ml drinks of water. To earn alcoholic beverages they would be required to repeatedly press the letters 'd' and 'r' a predetermined number of times, while water could be earned by pressing 'w' and 'a'. For each type of drink, the first earned beverage required 40 button presses. To earn subsequent drink of either kind the number of required button presses increased one-and-one-half times (i.e., 60, 90, 135, 203, 304, 456, 684 and 1,026, 1,538 clicks). Each type of drink required a total of 4,536 button presses to reach the maximum amount allowed (software for this task is available upon request to M.L.). Each session lasted until the maximum number of alcohol or water drinks were earned or to a maximum of two hours (excluding washroom breaks). While drinks could be earned and consumed at any time during the session, there was no requirement for participants to earn any drinks during the sessions and they were required to remain seated in the testing room until each session was completed. Each participant self-determined the rate of administration of all earned beverages, but new drinks of the same kind could not be earned until the previous drink had been completed. Upon completion of the PR task, participants were brought a meal and remained in the laboratory until their BAC reached 0.04. They were then safely escorted home by one of the researchers or by taxi.

Table 7.1. Timeline of procedures during both self-administration sessions.

Time of procedure	Tobacco and alcohol administration sessions
~5 minutes after arrival	Breath alcohol and carbon monoxide analyses
~10 minutes after arrival	Baseline VAS
~12 minutes after arrival	Alcohol and water presentation
~15 minutes after arrival	1st cigarette followed by VAS
Immediately after VAS completion	Prime dose of alcohol
10 min. after prime alcohol dose	Start of PR self-administration task
30 min. after start of 1st cigarette	2nd cigarette followed by VAS
60 min. after start of 1st cigarette	3rd cigarette followed by VAS
90 min. after start of 1st cigarette	4th cigarette followed by VAS
120 min. after start of 1st cigarette	End of PR self administration task

VAS = Visual Analog Scale. PR = Progressive Ratio.

7.4. Results

7.41 Alcohol and Water Self-Administration

Because the behavioural PR data increase geometrically, the data were screened for normality. Using the Kolmogorov-Smirnov method, it was determined that each PR distribution was satisfactorily normal (Ps>0.05) and this was confirmed through an inspection of the skewness and kurtosis of each variable (all absolute values < 2). To screen for outliers, Z-scores were calculated on the relative difference scores for PR responding in the two conditions (nicotine - denicotinized) and no outliers were identified (all absolute values < 3). Differences in the mean breakpoints for the number of button presses to earn alcohol and water drinks during the nicotine and placebo conditions were analyzed using a 2X2 ANOVA with drink type (water and alcohol) and cigarette type (nicotine-containing and denicotinized) as within-subjects factors. Figure 7.1 presents the PR data for earned alcohol and water during the two smoking conditions. There was a significant main effect of drink type ($F_{1, 14}$=8.79, P≤0.010) reflecting increased responding for alcohol relative to water. Analyses also revealed a trend toward a drink X cigarette interaction ($F_{1, 14}$=4.39, P≤0.055) suggesting a greater relative preference for alcohol during the nicotine condition.

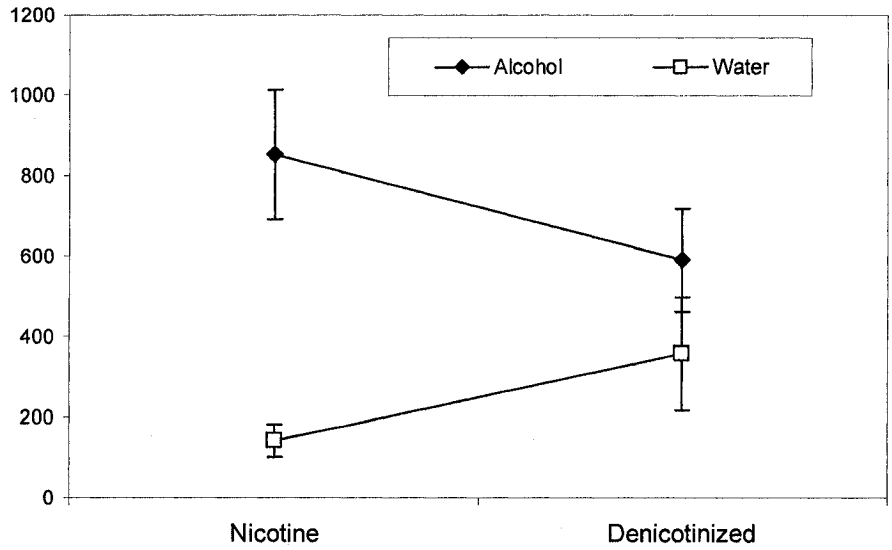

Figure 7.1. Mean PR break points for number of button presses to earn alcohol and water drinks during the nicotine and denicotinized tobacco conditions. Vertical bars represent ±SEM. Analyses revealed overall increased responding for alcohol relative to water ($P \leq 0.01$) as well as a trend toward a relative preference for alcohol during the nicotine condition ($P \leq 0.055$).

Table 7.2 presents the number of water and alcohol units consumed by each participant on each test day. Because statistical outliers were identified (absolute Z score > 3) in the relative changes in water (participant 7) and alcohol consumption (participant 12) during the two test conditions, these data were analysed using non-parametric Wilcoxon signed-rank tests. The analyses revealed that a significant proportion of participants increased alcohol consumption in the nicotine condition relative to the denicotinized condition ($Z=-2.13$, $p \leq 0.03$), while water consumption was not systematically different in the two conditions ($Z=-1.41$, $p \geq 0.16$) (Figure 7.2).

Table 7.2 Number of water and alcohol units consumed during PR task in the two conditions. Difference values reflect changes in consumption over the two sessions (nicotine-placebo). Partially completed units were weighted as ½ unit.

Subject	Units of water -nicotine	Units of water -placebo	Difference in water units consumed	Units of alcohol -nicotine	Units of alcohol -placebo	Difference in number of alcohol consumed
1	5	4	+1	8	5	+3
2	0	0	0	10	6.5	+3.5
3	0	0	0	10	10	0
4	4	3	+1	10	9	+1
5	0	0	0	10	8	+2
6	2	2	0	2	1	+1
7	0	10	-10	10	5	+5
8	7	9	-2	8	7	+1
9	6	6	0	8	6	+2
10	3	5	-2	0	0	0
11	0	1	-1	5	4	+1
12	4	3	+1	2	9.5	-7.5
13	5	6	-1	8	8	0
14	7	10	-3	7	6.5	+0.5
15	2	1	+1	10	8.5	+1.5

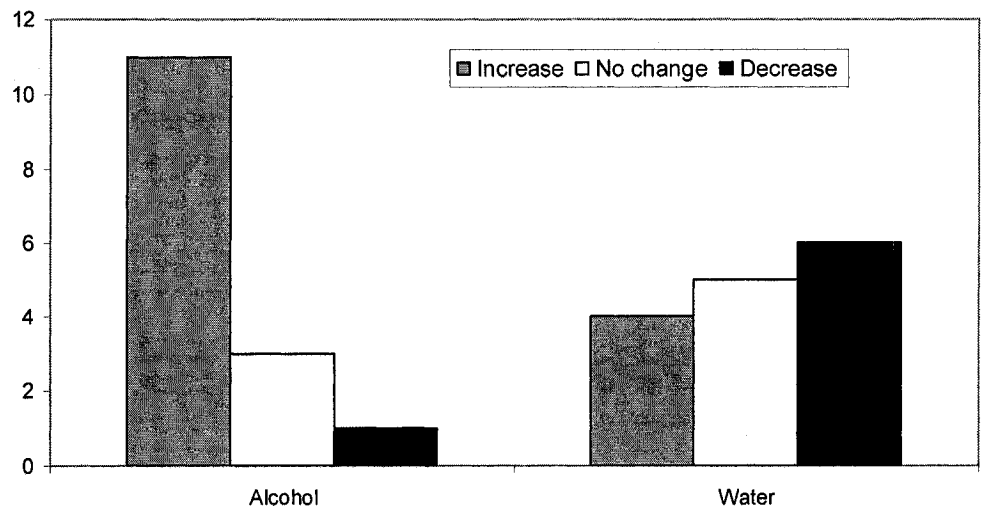

Figure 7.2 Number of subjects increasing, not changing, or decreasing alcohol and water ingestion during the nicotine test session. A significant proportion of subjects increased alcohol consumption in the nicotine condition, while water consumption was not systematically different in the two conditions.

7.42 Subjective Response to Smoking

The subjective effects of the nicotine and placebo cigarettes prior to alcohol consumption were examined by comparing the relative changes from baseline in each VAS score following the first cigarette of each test day using paired samples t-tests. One subject did not provide a post-cigarette rating for 'high' on one of the test days limiting analyses for this variable to fourteen participants.

Ingestion of the first nicotine cigarette was associated with significantly increased ratings of 'high' [$t(13) = 2.23$, $P \leq 0.044$], 'stimulated' [$t(14) = 2.55$, $P \leq 0.023$], 'sedated' [$t(14) = 3.06$, $P \leq 0.009$], and 'intoxicated' [$t(14) = 2.98$, $P \leq 0.010$] relative to the placebo cigarette. No systematic differences were evident for ratings of 'energetic', 'anxious', 'want alcohol', 'like cigarette', 'crave cigarette' or 'crave alcohol' (Ps >0.1). Because simultaneous nicotine-induced increases in 'stimulated' and 'sedated' were not expected, bivariate correlations were performed among the variables significantly affected by nicotine administration. Nicotine-induced changes in 'stimulated' and 'sedated' were not related to each other [$r=-0.015$; $P \geq 0.96$], but each was positively associated with change in 'intoxicated' [stimulated-intoxicated: $r=0.70$; $P \leq 0.004$; sedated-intoxicated: $r=0.53$; $P \leq 0.043$], suggesting that there may have been differences in how the participants interpreted nicotine's intoxicating effects. Nicotine-induced change in 'high' was not significantly correlated with change in 'intoxicated' [$r=0.44$; $P \geq 0.111$], 'sedated' [$r=0.43$;

P≥0.128] or stimulated [r=0.50; P≥0.067]. Changes in none of these variables were related to overall nicotine related changes in alcohol consumption [Rs<.2;Ps>0.5]. Relative differences in subjective responses following the initiation of alcohol consumption could not be meaningfully analysed because of substantial variability in both the rate and frequency of alcohol administration throughout the testing sessions.

7.43 Cigarette Administration

In order to determine if the rates of self-administration for the nicotine-containing and denicotinized cigarettes significantly varied a 2X2 repeated measures ANOVA was performed using time to complete each cigarette (1^{st}, 2^{nd}, 3^{rd}, 4^{th}) and cigarette type (nicotine-containing and denicotinized) as within subjects factors. There were significant main effects for time of cigarette completion ($F_{3,42}=11.77$, $P\leq0.001$), reflecting the tendency for the first cigarette of each test day to be completed more quickly than subsequent cigarettes, as well as for cigarette type ($F_{1,14}=21.91$, $P\leq0.001$) reflecting slower administration of the nicotine-containing cigarettes (Figure 7.3). The cigarette type by time to completion interaction was not statistically significant ($P>0.1$).

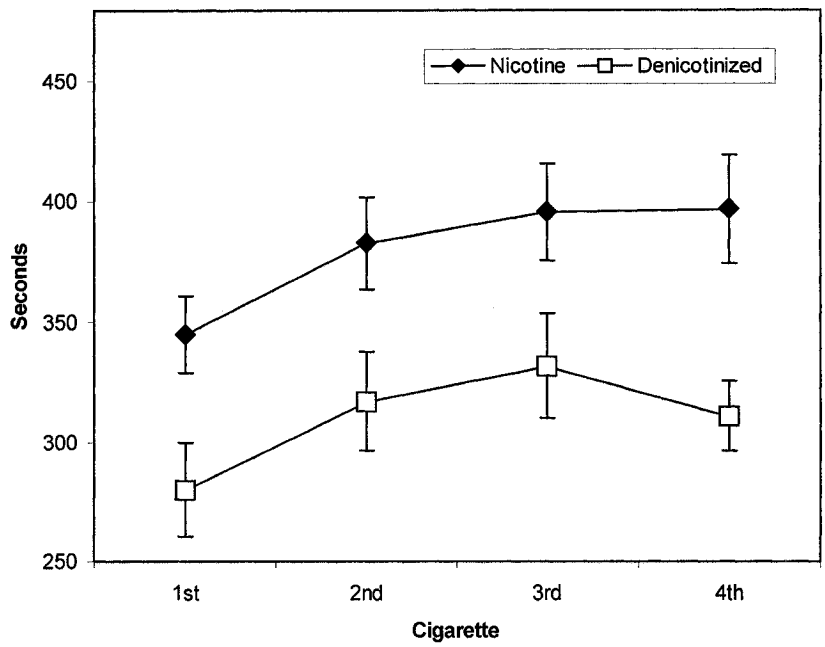

Figure 7.3 Mean time to complete each nicotine-containing and denicotinized cigarette in seconds. Vertical bars represent ±SEM.

Because VAS ratings were collected immediately following the completion of each cigarette, we performed a series of post-hoc stepwise regressions to determine if time to cigarette completion was associated with subjective state. For each cigarette, all corresponding subjective ratings were entered as potential predictors for the length of time of completion. For both the second ($r=.563$; $p<0.029$) and third ($r=.544$; $p<0.036$) nicotine-containing cigarettes the sole statistically predictor for time of cigarette completion was the respective 'intoxicated' rating, indicating that relatively high levels of intoxication were associated with a relatively slower pace of smoking. There

was also a significant association between time of completion of the final 'denicotinized' cigarette and the corresponding 'like drink' rating ($r=.614$; $p<0.015$), indicating that high levels of 'drink liking' were associated with a slower pace of smoking for this cigarette. No variables were found to be significantly associated with the time of completion of any of the other cigarettes ($Ps>0.05$).

7.5 Discussion

In this study, nicotine administration via tobacco smoke increased alcohol consumption in a significant majority of the participants. While these findings are consistent with data demonstrating increased overall levels of alcohol consumption among smokers (e.g., Batel et al., 1995), to our knowledge this is the first placebo-controlled study to demonstration that nicotine acutely increases alcohol ingestion in humans.

Although the present study did not directly assess the mechanisms underlying nicotine's ability to potentiate alcohol self-administration, nicotine may increase alcohol ingestion through a neuropharmacological action. The appetitive reinforcing properties of both drugs have been related to midbrain dopamine (DA) transmission (e.g., Di Chiara and Imperato, 1988), and evidence suggests that nicotine and alcohol may overlap in the mechanisms by which they promote DA release. In laboratory animals, both drugs appear to promote midbrain DA transmission through stimulation of nicotinic acetylcholine (NACh) receptors in the ventral tegmental area (e.g. Bolmqvist et al., 1997; Soderpalm et al. 2000; Tizabi et al. 2002) and the blockade of NACh receptors decreases alcohol self-administration in animals (Bolmqvist et al., 1996; Le et al., 2000) and alcohol drinking desire in humans (Chi and de Wit, 2003). Moreover, nicotine is also believed to enhance the DA response to other reinforcers by facilitating burst firing of the DA neurons (Rice and Cragg, 2004; Zhang and Sulzer, 2004) raising the possibility that nicotine

increases alcohol responding by potentiating alcohol-related DA reinforcement. Finally, noradrenaline transmission has also been proposed to affect alcohol ingestion (Amit & Brown, 1982; Le et al., 2005), and nicotine increases noradrenaline release as well (e.g. Grenhoff and Svensson, 1989).

An alternative means by which nicotine may affect alcohol administration is through a pharmacokinetic interaction. Evidence suggests that nicotine alters mechanisms involved in hepatic alcohol metabolism (Schoedel and Tyndale, 2003) as well as rates of gastric emptying (Gritz et al., 1988), factors that might alter alcohol absorption and distribution. However there is little direct empirical evidence to support this. Nicotine has failed to alter alcohol's pharmacokinetic properties in laboratory animals (Hisaoka and Levy, 1985; Collins et al., 1988) and evidence from human studies has been inconsistent (Perkins et al., 1995; Kouri et al., 2004). Thus there is currently insufficient evidence to definitively exclude or support a pharmacokinetic explanation for our findings.

A relatively unexpected finding in the present study was that cigarette administration rates varied both within and between conditions. Nicotine-containing cigarettes were smoked at a slower rate than denicotinized tobacco, and for both types of cigarettes the first cigarette was smoked significantly faster than all others (Figure 7.3). Although the relatively faster pace of denicotinized tobacco administration is consistent with previous research indicating that smokers modify their 'puffing' behaviour to achieve and

maintain desirable nicotine levels (for review see Scherer, 1999), because changes in smoking rates were approximately equivalent in both conditions, it is unlikely that within session differences can be solely explained by attempts to optimize nicotine levels. An alternative explanation is that alcohol-related effects and/or intake may have influenced smoking rates following the initiation of drinking. This possibility appears to be consistent with *post-hoc* findings that suggest the rates of administration of some cigarettes were associated with levels of intoxication (2^{nd} and 3^{rd} nicotine cigarette) or drink liking (4^{th} placebo cigarette). While concurrent access to alcohol may have contributed to the variability in smoking rates, allowing participants to choose when they wanted to drink relative to tobacco administration was important to ensure the ecological validity of the findings.

The present results should be interpreted in light of the following methodological considerations. First, because we wished to control for potential confounding effects of nicotine withdrawal, participants were minimally nicotine dependent and the degree to which these results are applicable to heavier smokers remains unknown. Alternative designs to test the effects of nicotine on alcohol self-administration in dependent smokers are clearly needed. Second, the present protocol only tested men and it is possible that the findings may not extend to women. Evidence suggests that women are less sensitive to the pharmacological effects of nicotine than men (Perkins et al., 2002; Perkins et al., 1999) and that smoking may differentially affect

alcohol consumption in men and women (Perkins et al., 2000). Additional research should be directed toward examining possible gender differences in alcohol-nicotine interactions. Third, since variability in the rate and frequency of alcohol self-administration was inherent in the research protocol, it was not possible to systematically assess the subjective effects associated with combined fixed doses of alcohol and nicotine. While previous research suggests that nicotine co-administration enhances several positive alcohol-related effects (Kouri et al., 2004; Perkins et al., 1995) as well as alcohol craving (Kouri et al., 2004) the present design did not allow us to determine how subjective effects were associated with changes in self-administration. It should be noted, however, that participants in the current study reported several discernable subjective effects of nicotine relative to placebo prior to alcohol ingestion including increased feelings of high, stimulation, and intoxication. Fourth, because the protocol imposed limits on the amount of alcohol consumed and the length of the drinking sessions it is possible that ceiling and floor limits may have influenced the magnitude of the observed effect. Indeed, in five of eleven cases where more alcohol was consumed during the nicotine than placebo condition, participants consumed the maximum possible dose during the nicotine session; among the three participants that ingested equal amounts of alcohol on both test days, one drank the minimum amount allowed on both days and a second consumed the maximum on both days. Nevertheless, despite this a significant majority of participants exhibited increased alcohol consumption during the nicotine

condition. Finally although the sample size in this study was modest (n=15), it was within the norms for investigations assessing within subject drug effects in humans and small sample size is typically associated with increased incidents of type II but not type I error.

In conclusion, to our knowledge, the present study is the first to demonstrate that nicotine administration via tobacco smoke increases alcohol self-administration in at least some smokers using a blinded placebo-controlled study. Because concurrent tobacco use may lead to alcohol dose escalation during drinking sessions, this practice may place some individuals at elevated risk for developing alcohol related problems. Future studies are needed to further delineate the effects and consequences of nicotine and alcohol co-administration and to extend these findings to other groups of smokers.

8. Abridging Statement to Study 4

Evidence that tobacco administration acutely increases alcohol self-administration is consistent with the hypothesis that alcohol co-administration with psychostimulant drugs may increase alcohol ingestion through a DAergic action. However because this study did not directly assess nicotine's effects on DA neurotransmission, the precise mechanisms involved in nicotine's augmentation of alcohol intake could not be definitively identified in the preceding investigation. In order to further examine the possible role of DA in mediating changes to alcohol self-administration, in study 4 we directly examined the effects of selectively decreasing DA availability on alcohol intake using a similar self-administration paradigm to that used in study 3.

9. The effect of acute dopamine precursor depletion on alcohol self-administration in men.

Sean P. Barrett[1], Robert O. Pihl[1,2], Chawki Benkelfat[2], Caroline Brunelle[1], Simon N. Young[2], Marco Leyton[2]

Departments of Psychology[1] and Psychiatry[2] McGill University, Montreal Canada

9.1 ABSTRACT: *Rationale and Objective:* Dopamine (DA) is believed to mediate aspects of human alcohol ingestion yet little is known about the degree to which this is affected by individual differences. This study sought to clarify DA's role in alcohol self-administration in a heterogeneous sample of non-dependent drinkers using the acute phenylalanine/tyrosine depletion (APTD) method. *Methods:* Sixteen men with variable individual and family drinking histories completed 4 testing sessions. In one session, cardiac responses to the acute ingestion of 0.75 g/kg of alcohol were determined. In 3 randomized double-blind sessions participants ingested a nutritionally balanced (BAL) amino acid (AA) mixture, a mixture deficient in the DA precursors, phenylalanine and tyrosine, and APTD followed by the immediate DA precursor L-DOPA (Sinemet, 2 x 100mg/25mg). Beginning 5 hours following each AA ingestion participants completed self-administration sessions where units of their preferred alcoholic beverage and glasses of water could be earned using a progressive ratio task. *Results:* Overall alcohol self-administration was reduced in both the APTD and APTD + L-DOPA conditions relative to the BAL condition. There were no significant differences in water administration among the AA conditions. Stepwise linear regressions were used to determine how the observed changes in alcohol self-administration were related to various alcohol-related variables. For both APTD and APTD+L-DOPA induced changes in alcohol self-administration the sole statistically significant predictor was ethanol-induced cardiac change. Post hoc analyses revealed a robust effect of AA condition on alcohol consumption in individuals with a

high cardiac response to ethanol ingestion but no differences in alcohol intake among those displaying a minimal cardiac response. *Conclusions:* The findings suggest that DAergic manipulations affect alcohol self-administration in a subset of drinkers, and that this may be predicted on the basis of their cardiac response to acute alcohol ingestion.

Keywords: alcohol, addiction, motivation, self-administration, dopamine, heart rate, progressive ratio.

9.2 Introduction

Like virtually every other addictive substance, alcohol administration increases dopamine (DA) neurotransmission in mesocorticolimbic regions (e.g., Samson et al 1992) an action believed to be involved in the reinforcing effects of various abused drugs including alcohol (Di Chiara & Imperato, 1988). In rodents, the initiation of alcohol ingestion is time-locked to increases in DA overflow (Weiss et al., 1992), and DA antagonists attenuate intake (Rassnick, 1992; Files et al., 1998). In humans, functional neuroimaging studies suggest that alcohol ingestion increases DA release (Boileau et al., 2003) while decreasing DA neurotransmission leads to overall reductions in alcohol self-administration in healthy social drinkers (Leyton et al., 2000a; Enggasser & de Wit, 2001) and in patients meeting criteria for alcohol dependence (Modell et al., 1993). Despite the consistency of these findings, DAergic reductions do not appear to decrease alcohol consumption in all subjects (Modell et al., 1993; Enggasser & de Wit, 2001) and a growing body of evidence suggests that DA's role in regulating alcohol intake may differ across drinking populations.

Several distinct alcoholism subtypes have been proposed (Windle & Scheildt, 2004; Babor et al., 1992; Cloninger, 1987) and numerous recent findings suggest a heterogeneous role for DA in alcohol reinforcement in different alcohol dependent populations. Genetic markers for separate DAergic and GABAergic pathways for alcoholism have been described (Noble

et al., 1998; Young et al., 2005) and neuroanatomical findings suggest that central DAergic abnormalities may not be evident in all alcoholics (e.g. Tupala & Tiihonen, 2004; 2005). Moreover, there is considerable variability in the response to pharmacotherapies that directly or indirectly target DA neurotransmission in the treatment of alcoholism (e.g. Walter et al., 2001) and relapse to drinking following administration of the DAergic drug flupenthixol has been proposed to be associated with the degree of DA involvement in alcoholic symptom presentation (Walter et al., 2001).

Evidence from non-dependent drinkers also suggests that there may be individual differences in the role of DA in alcohol reinforcement. For example, non-dependent heavy drinkers tend to experience more stimulant and less sedative alcohol-related effects relative to light drinkers (e.g. Holdstock et al., 2000; King et al., 2002) and it has been suggested that this may in part reflect a differential DAergic response to alcohol (King et al., 2002). It has also been proposed that individuals with an exaggerated heart rate (HR) response to the ascending limb of the blood alcohol concentration curve display an increased sensitivity to alcohol's DA effects and that a heightened HR response to alcohol may represent a peripheral marker to identify individuals that exhibit DA-specific alcohol reinforcement (Brunelle et al., 2004; Conrod et al., 2001). Although this hypothesis is supported by findings that alcohol-induced cardiac effects are proportional to both DA release (Boileau et al., 2003) and alcohol-related stimulant effects (Brunelle et al., 2005) direct evidence linking

alcohol's HR effects with its DA-mediated reinforcing effects is currently lacking. In an effort to better clarify DA's role in human alcohol self-administration, the present investigation examined the effect of decreasing DA neurotransmission on alcohol self-administration in a sample of non-dependent male drinkers who varied across a number of domains including current drinking patterns, individual and family drinking histories and alcohol-induced cardiac responsivity.

DA neurotransmission was decreased using the acute phenylalanine/tyrosine depletion (APTD) method (Moja et al., 1996; Sheehan et al., 1996; McTavish et al., 1999; Leyton et al., 2000b). APTD has been demonstrated to decrease extracellular DA levels in humans both during basal conditions (Montgomery et al., 2003) and in response to drug administration (Leyton et al., 2004a). APTD offers several advantages as a research tool. Because its behavioural effects develop within three hours and are transitory this technique can be used on an outpatient basis (McTavish et al., 2001a). APTD has also been demonstrated to be well tolerated in a variety of normal and clinical human populations (e.g. Leyton et al., 2000b; Mctavish et al., 2001) and it appears to be devoid of many side effects often associated with other treatments that reduce DA transmission. Moreover the neurochemical effects of APTD appear to be specific to the catecholamines, with the possible exception of some trace amines (Palmour et al., 1998; McTavish et al., 1999), and by acting pre-synaptically, APTD should decrease neurotransmission at all

DA receptor subtypes. In a condition, participants ingested both the APTD mixture and the direct DA precursor, L-DOPA. It was predicted that L-DOPA prevent effects of APTD.

9.3 Materials and methods

9.31 Participants

Male participants between the ages of 19 and 30 were recruited from the community through advertisements placed in local community newspapers and on university websites. An initial telephone interview excluded those with self-reported medical or psychiatric illness, with a history of adverse consequences from alcohol consumption, with current substance abuse or dependence, with a lack of familiarity with the alcohol doses to be administered or with insufficient knowledge about the history of alcohol-related problems in their biological relatives. Potential participants were told that the study would involve four full days of testing plus an additional half day for screening and that they would be required to remain abstinent from all prescription and illicit drugs throughout the duration of the study. Twenty-nine individuals meeting these criteria were invited to the laboratory to complete the full screening. All were assessed by a routine medical exam and standard blood work and all completed a psychiatric evaluation using a semi-structured clinical interview using DSM-IV criteria (First et al., 1995). Participants also completed the individual and parental form of the Michigan Alcoholism Screening Test (MAST, Pokorny et al., 1972; FMAST, MMAST, Crews and Sher, 1992), and provided further details about the alcohol use histories of all first- (parents and siblings) and second- (grandparents, parent's siblings and half-siblings) degree relatives using the Family History Research Diagnostic

Criteria (Andreasen et al., 1977). Eighteen individuals were deemed eligible to complete the study. Those invited to participate were medically healthy, were free of all current Axis I disorders including Major Depressive Disorder, Bipolar disorder, Psychosis, Psychoactive Substance Use Disorders, Panic Disorder, and Obsessive Compulsive Disorder, and were able to provide information about the presence or absence of current or past alcohol abuse or dependence in each of their first and second degree relatives. The study was carried out in accordance with the Declaration of Helsinki, and was approved by the McGill University Health Centre's Research Ethics Board. All subjects provided written, informed consent prior to their participation and were compensated C$210 upon completion of the protocol.

9.32 Amino Acid Administration

There were three test sessions where participants ingested AA mixtures. Each was conducted a minimum of three days apart, was double blind and in counterbalanced randomized order. Participants ingested APTD, APTD followed by L-DOPA/Carbidopa (100mg/25mg, administered p.o. at 1 and 3 hours after AA ingestion), or a nutritionally balanced mixture (BAL). On the APTD and BAL test days participants ingested identical looking placebo pills in lieu of L-DOPA/Carbidopa. The APTD mixture's composition, preparation and administration were based on a 102.3 gm balanced mixture with phenylalanine and tyrosine withheld (Young et al., 1985; Leyton et al., 2000b).

On the day prior to testing, participants were fed a low protein diet supplied by the investigators. They were also asked to refrain from drinking any alcohol on this day, to restrict themselves to 3 cups of caffeine containing beverages, and to fast from midnight. On the morning of each test day participants arrived at 8.30. At this time they provided a urine sample that was used to ensure that they were drug free (Triage^{TM} Panel for Drugs of Abuse, sensitive to cocaine, amphetamines, barbiturates, benzodiazepines, Δ^9-tetrahydrocanabinol, opiates, and phencyclidine. Biosite Diagnostics ©, San Diego, CA, USA) as well as a breath alcohol sample using an alco-sensor III intoximeter (Thomas Security, Montreal, Canada) to ensure alcohol abstinence.

9.33 Plasma Amino Acid Measurements

Plasma samples were collected at morning baseline as well as 4.5 hours post-AA ingestion. Plasma phenylalanine and tyrosine concentrations were determined by HPLC with precolumn derivatization and fluorometric detection. Plasma samples were missing from 8 of the 48 test days.

9.34 Alcoholic Beverages

Prior to the study, each participant selected an alcoholic beverage to consume on each AA test day. The beverage could consist of any 80-proof liquor (including preferred brand) and a non-alcoholic mixer, and the same beverage was to be consumed on all three test-days. Choice of alcoholic

beverage was restricted to 80-proof liquors due to the high variability in the alcohol contents of commercially available brands of beer, wines and coolers, and the only restrictions on the choice of non-alcoholic mixer was that it contained no caffeine or aspartame (which contains phenylalanine). Participants were informed that on each test day they would be required to consume a minimum of the equivalent of one standard drink containing 12 grams of alcohol, and that the maximum dose of alcohol that could be consumed on any day was 72 grams or the equivalent of 6-full standard drinks.

9.35 Alcohol Exposure and Administration

The alcohol administration phase of the study was scheduled to commence 5 hr after the AA ingestion to coincide with the time frame that other APTD pharmacological and behavioural effects have been observed (*e.g.,* McTavish et al., 2001; Harmer et al., 2001; Leyton et al., 2000b, 2004a). Fifteen minutes prior to each alcohol administration session participants were comfortably seated in a chair in front of a computer on a large table and were presented with a glass containing 100 ml of water. Participants were instructed to handle the glass, and were told to look at and smell the drink but not to consume any of it. After three minutes had elapsed the subject completed a subjective assessment. Approximately 7.5 minutes prior to alcohol administration participants were presented with their preferred alcoholic beverage (containing 12 grams of alcohol and 100ml of mix). Again they were instructed to handle the glass and were

told to look at and smell the drink but not to consume any of it and after three minutes had elapsed they completed another subjective assessment.

Following the cue exposure, participants were instructed to consume the previously presented alcoholic beverage within 10 minutes. This initial priming drink was included to measure responses to a fixed dose of alcohol, to normalize drinking in the laboratory, to model the influence of an initial drink on subsequent drinking behaviour in the self-administration paradigm, and to enable comparisons with other studies using a similar self-administration paradigm (Petrakis et al. 2002; Barrett et al 2005c).

9.36 Alcohol and Water Self-administration

Following the consumption of the first alcoholic drink, participants were given the opportunity to work on a computer to earn up to 10 mixed alcoholic drinks, each containing 6 grams of alcohol and 50 ml of mix and/or 10 100ml drinks of water using a progressive ratio (PR) task. To earn each alcoholic beverage participants were required to repeatedly press the letters 'd' and 'r' a predetermined number of times, while water was similarly earned using the letters 'w' and 'a'. For each type of drink, the first earned beverage required 40 button presses and the number of button presses required to earn each subsequent drink of the kind increased one-and-one-half times (i.e., 60, 90, 135, 203, 304, 456, 684 and 1,026, 1,538

clicks). Each type of drink required a total of 4,536 button presses to reach the maximum amount allowed. Each session lasted until the maximum number of alcohol or water drinks were earned or to a maximum of two hours. Participants were not required to earn any drinks during the sessions, but were required to remain seated in the testing room until each session was completed. Upon completion of the self-administration task, participants were brought a high protein meal and remained in the laboratory until their BAC reached 0.04. They were then safely escorted home by one of the researchers or by taxi.

9.37 Subjective State

Participants were administered visual analogue scales (VAS) immediately prior to ingesting the AA mixture, following water exposure, following alcohol exposure and then following every 12 grams of alcohol. Items were rated on a ten cm line labelled with the integers 1-10 and anchored with the words "least" and "most". Items included in the VAS were 'high', 'euphoric', 'sedated', 'intoxicated', 'rush', 'excited', 'anxious', 'energetic', 'mind racing', 'alert', 'like drink', 'want drink', 'urge for drink', 'desire drink', and 'crave drink'. In addition, the final 13 participants who completed the protocol also verbally rate their level of nausea immediately prior to receiving their priming dose of alcohol on each test day using a 10-point scale (1= not at all to 10= extreme). This

nausea measure was added to the protocol after a participant that withdrew from the study cited feelings of nausea as his reason for termination.

9.38 Alcohol induced cardiac reactivity

On a fourth test day, participants' cardiac reactivity to alcohol ingestion was measured. Participants arrived at the laboratory in the morning, having fasted a minimum of 4 hours and abstaining from alcohol for a minimum of 24 hours. A ten-minute sober baseline HR measurement was taken using the Polar S810 monitor (Polar electro, Finland). Participants then consumed 0.75 grams of pure ethanol per kg of body weight mixed with 5 parts orange juice separated into two glasses. The time interval for the ingestion of each glass was 7.5 minutes. Following a 15-minute wait, HR was again measured for 10 minutes (between 30-40 minutes post-onset of alcohol ingestion). During each HR measurement, the first five minutes were not used in the calculation of the average HR as they served to control for adjustment to the procedure. Participants were explicitly told to remain still, and compliance to this instruction was verified through observation via a camera placed in the testing room. Ethanol-induced cardiac change was calculated by subtracting the baseline HR value from the intoxicated HR value and the dividing the difference by baseline HR in order to produce a percent change value. This HR measurement procedure has been demonstrated to provide a reliable and valid index of ethanol-induced cardiac change in male social drinkers (Conrad et al., 2001; Brunelle et al., 2004).

9.39 Statistical Analyses

All data were analyzed using the statistical software package for the social sciences (SPSS), version 11.0. The primary outcome variables in this study were the number of button presses during the PR task to earn alcohol and water in each AA session. Because the behavioural PR data increase geometrically, these data were screened for normality using the Kolmogorov-Smirnov method prior to analyses, and it was determined that logarithmic transformations were necessary in order for each variable to satisfy the normality assumption. The data were initially analyzed using a 3x2 repeated-measures ANOVAs using AA condition (BAL, APTD, & APTD+L-DOPA) and beverage type (water & alcohol) as within subjects factors. Unless otherwise specified all other comparisons involving AA-specific effects were conducted using repeated-measures ANOVAs using AA condition (BAL, APTD, & APTD+L-DOPA) as the within subjects factor and pairwise comparisons were evaluated with Least Significant Difference tests. Step-wise linear regressions were used to examine how changes in alcohol self-administration in the APTD and APTD + L-DOPA conditions relative to the BAL condition were related to various alcohol-related variables. Correlations among the alcohol-related variables were evaluated with Pearson's correlation coefficient. Family-wise Bonferroni corrections were applied when related analyses were conducted on several variables.

9.4 Results

9.41 Participants

Sixteen participants (age: 21.8±3.3 years old) completed the entire protocol, and two discontinued during their first AA test day. One withdrew due to experiencing nausea following the ingestion of the AA mixture (APTD+L-DOPA) while the second participant withdrew after completing the BAL session, citing concerns about the dietary restrictions of the study. Table 1 presents the alcohol-related data for the participants completing the study. Although none met DSM-IV criteria for current alcohol abuse /dependence, as Table 9.1 shows individual and family drinking histories varied considerably.

Table 9.1. Individual and family drinking characteristics

Subject	Weekly alcohol drinks -current[1]	Weekly alcohol drinks -peak[2]	MAST	Alcohol dependent relatives[3]	Alcohol-induced cardiac change
1	6	18	0	0	+2.3%
2	7	7	0	0	+16.67%
3	7	7	0	0	+15.80%
4	2	8	0	0	+26.92%
5	20	20	0	3	+22.92%
6	3	24	0	3.5	-6.00%
7	13	30	0	0	+11.48%
8	8	18	0	0	+1.61%
9	13	30	0	3	+4.48%
10	14	28	0	2.5	+6.90%
11	18	48	5	3	+8.16%
12	16	30	4	2	+5.36%
13	2	24	2	0	+14.00%
14	17	18	0	0	+18.03%
15	9	24	2	3	+11.86%
16	9	26	0	0	+25.45%

[1]Reflects weekly drinking amounts over the preceding 30 days. [2] Reflects weekly drinking amounts during month of heaviest use. [3] Number of relatives with a lifetime diagnosis of alcohol dependence. First-degree relatives received a weight of 1 and second-degree relatives were weighted 0.5.

9.42 Amino Acid Depletion

Figure 9.1 presents plasma tyrosine and phenylalanine at morning baseline and 4.5 hours following ingestion of the AA mixture for each test day. Relative to the morning baseline the BAL mixture increased plasma phenylalanine by 237% and tyrosine by 166%. APTD decreased phenylalanine to 16% and tyrosine to 27% of morning levels. The administration of L-DOPA did not affect the degree of AA depletion produced by APTD.

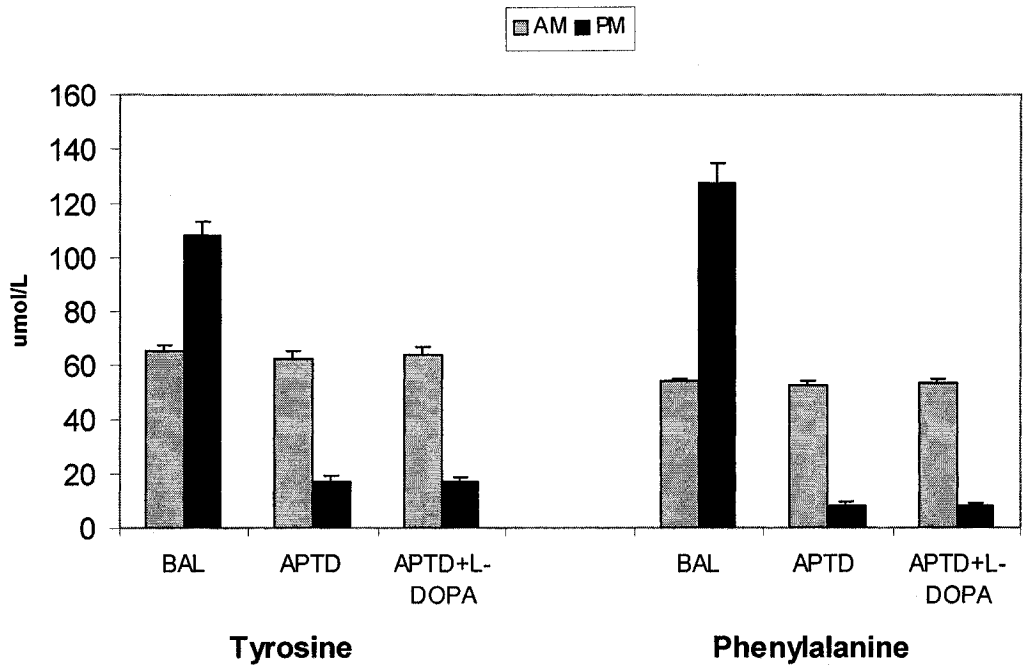

Figure 9.1: Plasma tyrosine and phenylalanine levels at morning baseline and 4 hours following AA ingestion each AA test condition.

9.43 Nausea

Analyses revealed no significant differences among the AA conditions in reported levels of nausea; $F(2, 24) = 1.34$, $p=0.281$.

9.44 Alcohol and Water Self-Administration

Analyses revealed main effects of AA condition beverage type $F(1, 15)=4.56$, $p\leq0.05$, as well as a significant AA condition X beverage type interaction $F(2,30)=3.52$, $p\leq0.04$ (Fig 2.) Because there appeared to be systematic differences in the administration of alcohol and water, additional analyses were performed considering each beverage type separately. There were no significant differences in water administration among the AA conditions ($F(2, 30)= .82$, $p\geq0.449$). There was however a significant main effect of AA condition for alcohol self-administration ($F(2, 30) =4.7546$ $p\leq0.016$), reflecting significantly greater alcohol intake on the BAL test session relative to the APTD ($p\leq0.03$) and APTD+L-DOPA ($p\leq0.01$) conditions. Beverage administration on the APTD and APTD+L-DOPA sessions did not differ significantly ($p\geq0.35$).

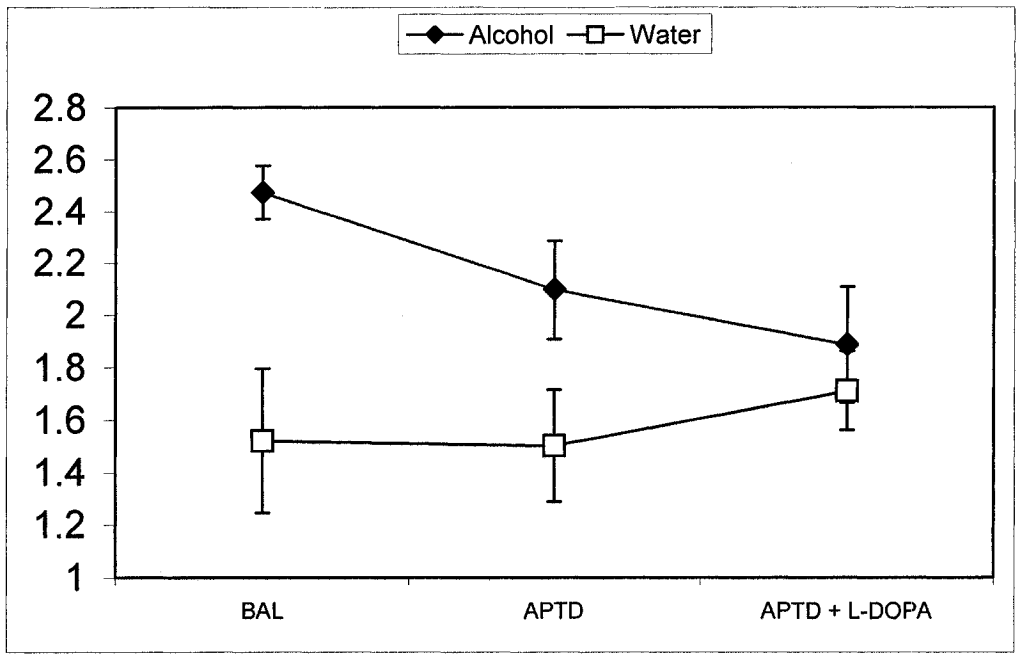

Figure 9.2. *Log transformed PR values for alcohol and water self-administration across AA conditions. Alcohol self-administration was significantly reduced in both the APTD and the APTD + L-DOPA conditions relative to BAL. Water administration did not significantly differ among the conditions.*

To determine whether the observed changes in alcohol self-administration were related to various alcohol-related variables stepwise linear regressions were performed using current and peak number of weekly alcoholic beverages consumed, number of first- and second-degree relatives with alcohol dependence, MAST score, and alcohol-induced HR change scores as potential predictor variables. For both APTD ($r=0.713$; $p\leq0.002$) and APTD+L-DOPA ($r=0.651$; $p\leq0.006$) induced changes in alcohol self-administration relative to the BAL condition the sole statistically significant predictor was ethanol-induced HR change. In order to verify specificity of

these relationships as well to determine the associations among the alcohol-related variables a series of Pearson's bi-variate correlations were performed. Because these analyses were preformed using 7 different variables the threshold for statistical significance was adjusted to $P \leq 0.007$ using a family-wise Bonferroni correction.

Results from the correlational analyses are presented in Table 9.2. Alcohol-induced HR change was associated with both APTD and APTD+L-DOPA induced changes in alcohol self-administration ($p \leq 0.007$). However no other variables were associated with change in drinking or with alcohol-induced cardiac change ($Ps \geq 0.09$). While there was a significant positive correlation between peak number of weekly drinks and MAST score, no other relationships exceeded the threshold for statistical significance ($Ps \geq 0.007$).

Table 9.2. Correlations among alcohol related variables.

	Weekly drinks -peak	MAST	Alcoholic Relatives	Alcohol cardiac change	Change in alcohol earned (APTD)	Change in alcohol earned (APTD+L-DOPA)
Weekly drinks -current	0.52*	0.30	0.41	0.06	-0.16	0.26
Weekly drinks -peak		**0.65****	0.56*	-0.36	-0.35	-0.05
MAST			0.36	-0.17	-0.08	-0.18
Alcoholic Relatives				-0.40	-0.40	-0.04
Alcohol cardiac change					**0.71****	**0.65****
Change in alcohol (APTD)						0.22

*$p \leq 0.05$, ** $p \leq 0.007$

To further examine the relation between ethanol-induced cardiac changes in alcohol self-administration, a median split of the ethanol induced cardiac change distributions was performed to create a group of high (n=8) and low (n=8) HR responders. High HR responders displayed a mean ethanol-induced HR increase of 19%(± 5.2%), while the low HR group had an average HR increase of 4.3% (±5.5). Repeated-measures ANOVAs were then performed to determine if these groups exhibited differential responses to the AA conditions. In high HR response group there was an overall effect of the AA condition on alcohol self-administration ($F(2, 14) = 4.41$; $p \leq 0.05$) with participants earning significantly more alcohol in the BAL condition relative to

either the APTD ($p \leq 0.017$) or APTD+L-DOPA ($p \leq 0.024$) conditions. In contrast, in the low HR response group no differences in alcohol self-administration were revealed among any of the AA conditions. Moreover, independent samples t-tests revealed that although the low HR group earned significantly greater quantities of alcohol during the APTD ($t=2.51$; $p \leq 0.024$) and APTD + L-DOPA ($t=3.00$; $p \leq 0.01$) conditions relative to the high HR group, there were no differences between the groups in alcohol self-administration during the BAL condition ($t=1.19$; $p \geq 0.25$) (Fig 9.3).

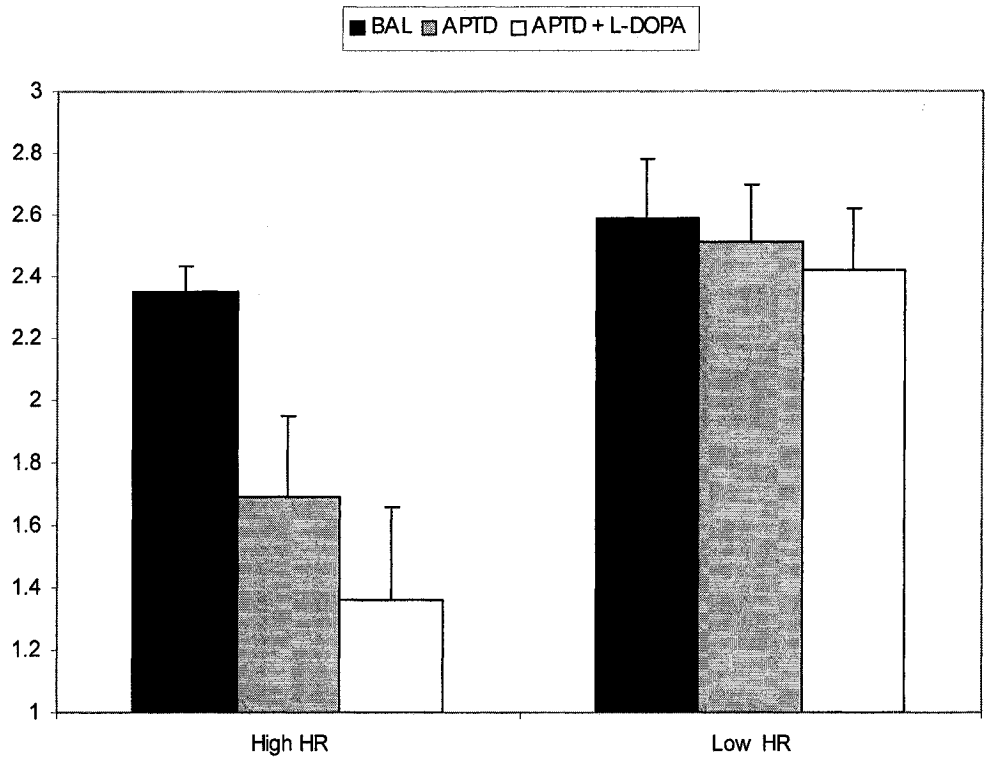

Figure 9.3: *Log transformed PR values for alcohol self-administration in individuals displaying high or low cardiac responses to acute alcohol ingestion. Participants with a high HR response to alcohol earned more alcoholic drinks on the BAL day relative to the APTD or the APTD+L-DOPA test days. No differences in alcohol self-administration were evident in low HR responders.*

9.45 Subjective Effects

Changes in VAS subjective ratings were analysed using 4x3x2 ANOVA using time (baseline, post water cue, post alcohol cue, post alcohol consumption), and AA condition (BAL, APTD & APTD + L-DOPA) as within subjects factors and HR group (high, low) as a between subjects factor. Because this analysis was performed on 14 different variables the threshold for statistical significance was adjusted to $P \leq 0.004$ using a family-wise Bonferroni correction.

VAS ratings were not significantly associated with HR group or AA condition and there were no significant AA x HR, AA x Time, HR x Time or AA x HR x Time interactions for any of the VAS measures. A number of VAS ratings were significantly affected by the cue exposures and alcohol administration. Significant main effects of Time for 'High', and 'Euphoria' each reflected elevated ratings of these variables post-alcohol ingestion relative to the two cue exposure ratings, while an effect for 'Intoxicated' resulted from an increased rating post-alcohol ingestion relative to each of the three other time points. The main effect for 'Desire Drink' reflected increased ratings following alcohol cue exposure and consumption relative to baseline and water cue exposure. Finally ratings for 'Sedation' were significantly elevated at morning baseline relative to each other time point, while the main effect for excited reflected decreased ratings following the water cue exposure relative to baseline, post alcohol cue exposure and post alcohol ingestion.

9.5 Discussion

In this study APTD significantly decreased alcohol self-administration in men, an effect that was proportional to participants' HR response to acute alcohol ingestion. While previous studies have reported decreased alcohol reinforcement following disruption of DA functioning (Modell et al., 1993; Enggasser & de Wit, 2001; Leyton et al., 2000a), to our knowledge this is the first study to identify an individual difference that is associated with a differential sensitivity to the DAergic manipulation. These results are consistent with the hypothesis that the neurobiological mechanisms affecting susceptibility to alcohol abuse are different in separate populations. The present results suggest that alcohol-induced changes in DA transmission may be especially relevant for individuals with elevated DA cell reactivity, as indexed by a heightened cardiac response to alcohol. In comparison, DA may have much less importance for alcohol self-administration in drinkers with a minimal cardiac response to alcohol ingestion.

Cardiac response to acute alcohol ingestion has been proposed to be an index of alcohol-related DA reinforcement (Conrod et al., 2001, Brunelle et al., 2004, Brunelle et al., 2005) and a recent functional neuroimaging study suggests that individual differences in alcohol-induced increases in HR are correlated with changes in alcohol-induced changes in DA neurotransmission (Boileau et al., 2003). In the present study ethanol-induced HR response was the sole alcohol-related variable to predict reduced alcohol self-administration

following DA depletion suggesting that HR response to acute alcohol ingestion may be a marker for the degree to which motivation to drink alcohol is dependent on DAergic mechanisms. Because the present study used a standardised method for determining alcohol-induced cardiac change that involved the administration of a relatively high dose of alcohol (Brunelle et al., 2005; Brunelle et al., 2004; Boileau et al., 2003; Conrod et al., 2001) a separate test day was required for HR measurement and we did not directly assess the effect of DA depletion on alcohol-induced cardiac change in the present protocol. Nevertheless reports that both the DA D2 antagonist haloperidol (Enggasser & de Wit, 2001) and the opioid receptor antagonist naltrexone (McCaul et al., 2001) attenuate alcohol-induced HR increases are consistent with the hypothesis that there is a direct relationship between DA neurotransmission and alcohol-related HR response.

While the present findings suggest that HR response to alcohol may be a marker for DA-specific alcohol reinforcement, they also indicate that the degree of DA involvement in alcohol reinforcement may not in and of itself be predictive of problematic drinking. Both HR response to alcohol and change in drinking following DA depletion, were unrelated to numerous indices of alcohol dependence risk including current and peak-drinking amounts, past alcohol related problems and family history of alcoholism. Nevertheless because DA depletion appeared to decrease alcohol self-administration in individuals with a high HR response to alcohol irrespective of other individual

differences, problematic drinkers with an elevated cardiac response to alcohol ingestion might especially benefit from treatments that target DA neurotransmission.

In the present study we used APTD to decrease DA synthesis. This method has been previously demonstrated to significantly decrease DA release in humans (Montgomery et al., 2003; Leyton et al., 2004a) and it has been demonstrated to be a sensitive tool for measuring DA-related drug effects. For example, APTD has been previously shown to decrease stimulant effects of amphetamine (McTavish et al., 1999b; McTavish et al., 2001), to decrease cocaine- and cocaine cue-induced craving (Leyton et al., 2004b), and to reduce alcohol self-administration in female social drinkers (Leyton et al., 2000b). Although the current findings extend these previous results and further validate APTD as a tool for investigating DA in human drug reinforcement, they also call into question the ability of L-DOPA to reverse APTD-related effects. Although L-DOPA was initially hypothesised to attenuate the effects of APTD on alcohol self-administration, there actually appeared to be a trend towards it increasing the magnitude of the APTD effect. Interestingly, similar results were recently reported in a study examining the effect of APTD on cocaine craving (Leyton et al., 2004b). While such findings are consistent with evidence that acute L-DOPA administration decreases DA cell firing in animals with compromised DA function (Harden & Grace, 1995; Robinson et al., 2004) because the present protocol did not directly assess the effect of

APTD + L-DOPA on DA function, the nature of interaction must remain speculative.

The present results should be interpreted in light of the following considerations. First, APTD might decrease norepinephrine (NE) synthesis (Palmour et al., 1998; though see McTavish et al., 1999), and it is possible that the observed effects on alcohol administration in part reflect changes to NE neurotransmission. However, because abundant evidence suggests that DA is more involved in alcohol and drug self-administration than NE (e.g. Wise, 1996) this does not seem likely. Second, the present protocol only tested men and it is possible that the findings may not extend to women. In a previous study of female social drinkers APTD was shown to reduce alcohol self-administration (Leyton et al., 2000a), however the degree to which this associated with cardiac response to ethanol remains unknown. Third, since there was considerable variability in the rate and frequency of alcohol self-administration in the research protocol, it was not possible to systematically assess the effect of APTD on alcohol effects following the priming dose. While previous research suggests that decreasing DA function may affect several alcohol-related effects (e.g. Enggasser & de Wit, 2001) the present design did not allow us to determine if changes in self-administration were systematically related to changes in the subjective effects of alcohol in dose ranges normally administered by most participants. Fourth, although the sample size in this study was modest (n=16), it was within the norms for investigations assessing

within subject drug effects in humans and small sample size is typically associated with increased incidents of type II but not type I error. Nevertheless, because we wished to examine APTD effects in a heterogeneous sample of drinkers it is likely that certain subtypes of non-dependent drinkers were not adequately represented by this small sample. Further research is clearly needed to delineate the role of DA in alcohol self-administration in different alcohol consuming populations.

In conclusion, DA precursor depletion decreased alcohol self-administration in a subset of non-dependent male drinkers and this was predicted by cardiac responses to acute alcohol administration. These findings suggest that among some drinkers DA may play only a limited role in alcohol reinforcement and highlight the importance of considering individual differences in determining treatments for alcohol misusing populations.

10. General Discussion

The main novel findings presented in this dissertation are that 1) when appropriate interview techniques are used polysubstance users appear to be able to reliably recall details of the order and amounts of all substances used on a particular occasion; 2) most substances appear to be routinely administered in a simultaneous polysubstance use context and some substances appear to co-administered in a systematic fashion; 3) alcohol is commonly concomitantly used with various psychostimulant drugs that are known to affect DA neurotransmission and when it is used with these substances drug users retrospectively report consuming greater than normal volumes of alcohol; 4) under blinded placebo controlled conditions the psychostimulant nicotine increases alcohol ingestion in humans; and 5) decreasing DA function reduces alcohol ingestion in a subset of drinkers who are thought to display a heightened sensitivity to alcohol's DA-related effects. Collectively these findings suggest that examining patterns of simultaneous multiple substance use may provide insight into the mechanisms underlying certain addictive processes and that for the case of alcohol, drinkers may co-administer DAergic substances in order to achieve specific neuropharmacological effects.

In studies 1 & 2, simultaneous polysubstance use patterns were elucidated in two different drug-using populations and high rates of drug mixing were documented in each. In both studies the majority of users of every drug reported the simultaneous administration of additional substances and for most substances (i.e. ecstasy, cocaine, amphetamine, LSD, psilocybin, ephedrine, ketamine, GHB, mescaline) a minimum of 80% of users reported co-administering at least one additional substance during their most recent use of the substance. Because most drugs appear to be routinely co-administered with others, and this practice may alter a drug's behavioural and /or subjective effects (e.g., Barrett et al., 2003c; Pennings et al. 2002; Leri et al., 2003), it is possible that concomitantly used substances might contribute to the abuse liability of a given drug. As study 3 demonstrates, even a drug with seemingly innocuous intoxicating effects such as nicotine might affect the reinforcing effects of a co-administered substance and such findings highlight the importance of considering co-administered substances as potentially contributing to the aetiology and maintenance of various forms of substance use.

Not only do certain substances appear to be frequently co-administered with each other, but in many cases their patterns of concomitant use appeared to follow a particular sequence of administration. For example, when amphetamine was co-administered with MDMA, its use was reliably reported to precede ecstasy administration and when alcohol was used in combination

with most other substances (cannabis, psilocybin, MDMA, cocaine, amphetamine, methylphenidate and LSD) its initial use was reliably reported to precede the onset of other substance intake. Although reason (s) for these particular orders of administration were not directly examined, the description of relative drug taking sequences is potentially important both for designing ecologically valid research protocols that examine drug interactions as well as for determining the clinical importance of current research findings. For example, recent animal evidence suggests that the neurotoxic effects associated with MDMA-amphetamine co-administration are more pronounced when MDMA is administered prior to amphetamine (Clements et al. 2005), however this finding may be of only limited clinical significance since this does not appear to be a common pattern of administration for these drugs (Barrett et al., 2005b). On the other hand evidence that prior (but not subsequent) alcohol administration in cocaine users leads to increased plasma cocaine levels in humans (Perez-Reyes, 1994) may be more important to understanding the nature and consequences of alcohol-cocaine interactions since alcohol appears to be routinely administered prior to the onset of cocaine consumption.

While initial alcohol consumption appears to precede the intake of most concomitantly administered substances, when it is used with various psychostimulant drugs (i.e. cocaine, amphetamine, methylphenidate) alcohol ingestion appears to reliably resume following drug administration and evidence from both the retrospective and prospective studies reported in this

dissertation suggest that alcohol co-administration with various psychostimulant drugs is associated with increased levels of alcohol consumption. In study 2 both cocaine and methylphenidate users retrospectively reported consuming greater than normal amounts of alcohol in the presence of these drugs, while in study 3 nicotine was demonstrated to increase alcohol self-administration using a double-blind placebo controlled procedure.

Because each of these psychostimulants is believed to increase DA neurotransmission (e.g. Di Chiara & Imperato, 1988; Volkow et al., 1995; Pontieri et al., 1996), and DA is believed to mediate alcohol's ascending limb reinforcing effects (e.g. Fromme et al., 2003; Pihl & Peterson, 1995; Ollat et al., 1988) it is proposed that alcohol-psychostimulant co-administration may result in a DAergic neuropharmacological interaction that leads to alcohol dose escalation. This interpretation appears to be consistent with a number of observations. For example, although alcohol has been shown to affect the pharmacokinetic properties of both cocaine (e.g. Cami et al., 1998) and methylphenidate (Patrick et al., 1995), there do not appear to be significant pharmacokinetic interactions between nicotine and alcohol (Collins et al., 1988; Benowitz et al., 1986; Kouri et al., 2004) suggesting that any similarities in the interaction effects of these drugs with alcohol are likely not (solely) due to common pharmacokinetic effects. Moreover, evidence also suggests that the co-administration of any of nicotine, cocaine or methylphenidate augments

alcohol's subjective stimulant-effects and attenuates its subjective sedative effects (e.g. Pekins et al. 1995; Perez-Reyes & Jeffcoat, 1992; Barrett & Pihl, 2002), while alcohol's DAergic effects have been associated with both subjective stimulation (e.g. Newlin & Thomson, 1990; King et al., 2002) and continued alcohol ingestion (e.g. Weiss et al., 1994), and its sedative effects are believed to be most salient following the termination of DA release (e.g. Lewis & June, 1990). Finally there are several reports that selectively decreasing DA neurotransmission decreases human alcohol consumption (Leyton et al., 2000; Enggasser & de Wit, 2001; Modell et al., 1993). Although the results of study 4 suggest that only a subset of drinkers who display heightened ascending limb alcohol induced cardiac reactivity may be sensitive to such alterations in DA neurotransmission, we (Brunelle, Barrett & Pihl) have recently demonstrated that tobacco, cocaine and amphetamine users tend to have significantly elevated ascending limb heart rate responses to alcohol relative to non-users of the drugs (unpublished data currently in preparation). These results suggest that alcohol's DAergic effects may be of particular importance to psychostimulant users' drinking motives.

While evidence presented in this dissertation suggests that examining patterns of concomitant multiple substance use may help provide insight into the mechanisms underlying certain addictive processes, there remain a number of methodological challenges to developing scientifically rigorous, yet ecologically valid research protocols for examining the patterns and

consequences of simultaneous polysubstance use. In order to make meaningful measurements it is often necessary to impose a degree of experimental control over some of the variables of interest, and doing so might affect the phenomenon under investigation. Because in studies 3 & 4 we were primarily interested in patterns of alcohol self-administration we allowed participants a considerable degree of freedom in self-determining the pace, timing and amount of alcohol to be consumed (albeit using a highly controlled method to 'earn' the substance). However by not controlling these variables we compromised our ability systematically to measure subjective and behavioural effects associated with specific dosages. In addition had we not imposed controls over the administration of the other pharmacologic agents in these studies the alcohol self-administration data may not have been interpretable. While such considerations highlight the importance of having an a priori knowledge of the substance use patterns of the population of interest when designing experimental protocols, the use of retrospective methods to collect such descriptive data may be subject to reporting bias and certain details such as orders and amounts of substances typically consumed are not easily verifiable through the use of more objective measures. Nevertheless despite such potential methodological limitations in the present series of studies there appeared to be a high level of concordance between the findings of the retrospective and prospective approaches (i.e. with both methods alcohol administration was similarly affected by drugs with similar properties). Given the frequency of concomitant drug administration and its potential importance

for understanding addictive processes, continued efforts are clearly needed to devise reliable and valid methods for examining the patterns and consequences of simultaneous polysubstance use.

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Appendix 1:

Hallucinogenic drugs attenuate the subjective response to alcohol in humans

HUMAN PSYCHOPHARMACOLOGY
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Hallucinogenic Drugs Attenuate the Subjective Response to Alcohol in Humans

SEAN P. BARRETT*, JENNIFER ARCHAMBAULT, MARLA J. ENGELBERG and ROBERT O. PIHL
Department of Psychology, McGill University, Montreal, Canada

This study investigated possible interactions between alcohol and hallucinogens in 22 lysergic acid diethylamide (LSD) and/or psilocybin users through retrospective structured interviews. Of those who had used LSD with alcohol, 86·7 per cent reported a complete blockade of subjective alcohol effects, while the remaining cases reported a diminished response. In addition, 60 per cent of respondents who had used alcohol and psilocybin together reported a partial antagonism of subjective alcohol effects. *T*-test analyses revealed that LSD's antagonism of alcohol effects were significantly greater than those associated with psilocybin. It is proposed that LSD's effect on alcohol intoxication may involve interactions with various serotonergic and/or dopaminergic receptor systems. Copyright © 2000 John Wiley & Sons, Ltd.

KEY WORDS — lysergic acid diethylamide; alcohol; psilocybin; hallucinogens; serotonin; dopamine

INTRODUCTION

The therapeutic use of lysergic acid diethylamide (LSD) has been studied extensively as a possible adjunct to psychotherapy for the treatment of alcoholism (e.g. Abraham *et al.*, 1996; Mangini, 1998). Such studies have produced inconsistent results and this area of research was abandoned in the early 1970s due to concerns over LSD's safety (Mangini, 1998). Despite the fact that several clinical trials were conducted over a 25-year period, the effects of the combined use of alcohol and LSD were never elucidated. Nevertheless, the pharmacological profiles of these two substances suggest the possibility of a clinically significant interaction. For example, LSD binds with high affinity at both 5-HT_1 and 5-HT_2 receptors (e.g. Peroutka, 1994), and drugs that act on either of these receptor subtypes have been shown to alter both ethanol intake and discriminative stimulus effects in rats (Szeliga and Grant, 1998; Kostowski and Bienkowski, 1999). Furthermore, LSD is thought to act as a partial agonist at dopamine (DA) receptors (Watts *et al.*, 1995; Giacomelli *et al.*, 1998), and mid-brain DA transmission has been implicated in several of alcohol's reinforcing properties (e.g. Koob *et al.*, 1998). Given the fact that LSD is known to affect neural systems implicated in ethanol intake, reinforcement, and discriminative stimulus, one might expect the subjective human response to ethanol to be altered by LSD administration. Interestingly, a recent study of the drug taking patterns of adolescent drinkers suggests that the simultaneous use of alcohol and hallucinogens is quite common, with 16 per cent of the sample reporting combining alcohol with hallucinogens on at least one occasion (Martin *et al.*, 1996). The current investigation presents systematically collected information from individuals who have reported using ethanol with LSD and/or psychotic mushrooms, a related hallucinogenic drug.

METHODS

Participants for this retrospective self-report study were recruited through the 'snowball' method of sampling. This sampling method has been widely used to study hidden or clandestine populations

* Correspondence to: S. P. Barrett, Department of Psychology, McGill University, 1205 Dr. Penfield Avenue, Montreal, QC, Canada H3A 1B1. Tel: 514-982-5013. Fax: 514-398-4896. E-mail: barrett@ego.psych.mcgill.ca

(Jackson, 1997), and requires the researcher to make an initial set of contacts and to ask these contacts to introduce him/her to potential participants. In the present study four contacts whose past hallucinogenic use was known *a priori* were used to recruit subjects. Potential participants were contacted either in person or by telephone and were asked if they would answer some questions about their alcohol and drug use for a scientific study. Of the 25 individuals contacted, three declined to participate, leaving a final sample of 22 subjects.

Structured interviews were conducted orally and recorded via audio-tape. Participants were assured of their anonymity and informed that their audiotaped responses would remain strictly confidential. The interview consisted of a series of standardized open-ended questions designed to elicit information about the participant's previous experiences with alcohol, LSD, and psilocybic mushrooms when used alone or in combination. In order to avoid any possible investigator influence, all questions about possible alcohol/hallucinogenic interactions were always phrased as follows: have you ever used alcohol while under the influence of LSD (magic mushrooms) or LSD (magic mushrooms) while under the influence of alcohol? Did you notice any difference in the effect of either the alcohol or the LSD (magic mushrooms) when you used the two together? What was the nature of the difference? Can you give me a specific example about a time when this happened? In order for a report to be considered usable, the subject had to have used at least the minimum dose required to detect the subjective effects of each drug when used alone.

Reported drug interaction effects were rated by the principal investigator and by an independent rater who was blind to the study's hypotheses. Discrepancies in the coding were resolved by having a second independent rater score any interviews in question. Using a five-point Likert scale (1 = completely blocked, 2 = somewhat diminished, 3 = neutral, 4 = somewhat enhanced, 5 = strongly enhanced), the raters first scored the reported effect of alcohol when it was taken with LSD. Using the same Likert scale, the raters then coded the reported effect of LSD when it was taken in conjunction with alcohol. Ratings of reported effects of alcohol and psilocybin when the two drugs were used in combination were assessed in the same manner. Raters were instructed to eliminate cases in which interviewer bias was present. A complete transcript of all interviews is available from the authors upon request.

RESULTS

Nineteen males and three females were interviewed for the present study. The participants ranged in age from 18 to 28 years ($M = 23{\cdot}73$, $SD = 2{\cdot}86$). Most participants reported extensive past use of hallucinogens, with 73 per cent of subjects reporting 20 or more lifetime uses of LSD and 73 per cent reporting 20 or more lifetime uses of psilocybin. Drug interaction effects were not analysed for four subjects who reported that they had never used intoxicating levels of alcohol in combination with either LSD or psilocybin and for one participant who provided inconsistent, and thus uncodable, responses to interview questions. Only partial effects were analysed for two subjects who reported never having used intoxicating levels of alcohol with LSD, and for two subjects who reported never having used intoxicating levels of alcohol with psilocybin.

Pearson correlation coefficients were calculated in order to determine the inter-rater reliabilities for the coding of the interviews. These analyses revealed a very high concordance between raters for both LSD–alcohol interactions ($r = 0{\cdot}985$, $p < 0{\cdot}001$) and psilocybin–alcohol interactions ($r = 0{\cdot}871$, $p < 0{\cdot}001$). An analysis of the interview ratings revealed a striking antagonism of subjective alcohol effects when it was used in combination with LSD (see Table 1). Specifically, 86·7 per cent of the sample reported experiencing a complete blockade of subjective alcohol effects, while the remainder reported a diminished effect. No differences in subjective LSD effects were associated with alcohol use in any of the subjects. There was also a weaker tendency for subjects to report a diminished effect of alcohol when used in conjunction with psilocybic mushrooms, with 60 per cent of the sample noting a diminished effect, 34 per cent reporting no change and 6·7 per cent reporting an enhanced effect. The majority of the sample (80 per cent) also reported no change in psilocybin's effects when it was used with alcohol. However, two subjects reported a diminished effect, and one subject reported an enhanced effect of psilocybin when used in combination with alcohol. In addition, one participant voluntarily reported experiencing a pleasant synergistic effect when taking psilocybin with alcohol, while another participant reported having a very unpleasant synergistic effect.

In order to compare the effects of LSD and psilocybin on the subjective response to alcohol, a paired samples *t*-test was performed. This analysis revealed that LSD's antagonism of the alcohol

Table 1. Subjective effects associated with concurrent use of alcohol and hallucinogens

Id	Age	Sex	Estimated lifetime use of LSD	Estimated lifetime use of psilocybin	Concurrent use of alcohol and LSD		Concurrent use of alcohol and psilocybin	
					Subjective alcohol effects	Subjective LSD effects	Subjective alcohol effects	Subjective psilocybin effects
A	21	M	100–150	50–100	blocked	no change	no change	no change
B	26	M	20	20	blocked	no change	no change	no change
C	21	M	50	40–50	–	–	diminished	diminished
G	25	M	60–90	60–90	blocked	no change	diminished	no change
H	27	F	60–75	30–35	blocked	no change	–	–
I	28	M	30–50	20–30	blocked	no change	diminished	no change
J	24	M	25	50	blocked	no change	no change	no change
K	28	M	10–25	10–25	blocked	no change	diminished	no change
L	25	M	35	50	diminished	no change	diminished	no change
M	24	M	40	50	blocked	no change	no change	no change
P	24	M	>50	30–40	–	–	diminished	no change
R	24	F	30	2	blocked	no change	–	–
S	23	F	3	30	blocked	no change	no change	diminished
T	24	M	25	30	blocked	no change	enhanced	enhanced
U	26	M	200–300	50	blocked	no change	diminished	no change
V	28	M	25	50	blocked	no change	diminished	no change
W	22	M	15	30–35	diminished	no change	diminished	no change

effect is significantly greater than that associated with psilocybin $t(12) = 5{\cdot}741$, $p < 0{\cdot}001$.

REPRESENTATIVE SUBJECTIVE REPORTS

LSD–alcohol interactions

G, a 25-year-old male, reported extensive experience with LSD, using it on 60–90 separate occasions. Typically, G can begin to discern the effects of alcohol after four drinks and it takes approximately seven or eight drinks for G to become significantly intoxicated. According to G, 'When I was on LSD I found that no matter what quantity of alcohol I consumed on the high, I did not notice any of the effects of the alcohol'. G recalled one specific occasion when he drank approximately 12 beers over the course of an evening after ingesting LSD: '... at that point, I didn't notice the effects of the alcohol at all. I was not drunk, nothing. I just felt a little bloated.'

H, a 27-year-old female, reported extensive experience with LSD, using it on between 60 and 75 separate occasions. She reported using an intoxicating dose of alcohol (more than seven drinks) in combination with LSD 'several' times. According to H, LSD–alcohol interactions work two ways. 'The first example would be if I were to use LSD and then drink, I wouldn't feel any of the effects of alcohol until after the effects of the LSD had worn off... and if I were to take LSD once I was already subjectively feeling drunk, the alcohol effects would go away after taking the LSD.'

T, a 24-year-old male, reported using LSD on 25 occasions. T reported that there were several occasions where he consumed an intoxicating dose of alcohol (more than six drinks) while under the influence of LSD. According to T, 'You can't get drunk when you are on LSD ... One time I drank about 18 beers, a half bottle of Bailey's and a Mickey of vodka on two hits of acid and I didn't feel anything from the booze... it was just a normal LSD high.'

Psilocybin–alcohol interactions

B, a 26-year-old male, has used psilocybic mushrooms on 20 separate occasions. When using alcohol concurrently with psilocybic mushrooms, B claims that 'I could feel a combination of both. It is not like LSD where the alcohol effects are blocked. Sometimes one would be stronger than the other,

but that would just depend on how much I took of each'.

L, a 25-year-old male, has used psilocybic mushrooms on 50 separate occasions. According to L, when using psilocybin with a normally intoxicating dose of alcohol (more than four drinks), '... it produces a more mellow buzz. The alcohol effect was deadened'. When asked to compare this experience with that of LSD, 'I could feel the alcohol more for sure on mushrooms'.

V, a 28-year-old male, reported 50 previous uses of psilocybic mushrooms, including several occasions where he consumed a normally intoxicating dose of alcohol (more than six drinks). According to V, when using alcohol and psilocybic mushrooms together: 'You can tell that you've drunk alcohol when on mushrooms, but there would be less of an effect ... you could feel it more than when on LSD'.

DISCUSSION

The present data indicate that the subjective response to ethanol is strongly attenuated by the administration of LSD. Of the 15 LSD users who reported concurrent use of alcohol, 13 reported a complete blockade of alcohol's subjective effects, while the remaining two cases reported experiencing a virtual elimination of subjective alcohol effects when the drug was combined with LSD. The finding that LSD's antagonism of alcohol's effects reportedly occurred irrespective of whether the subject had consumed LSD prior to drinking or the LSD was ingested when already intoxicated further supports the conjecture that LSD's effect on the subjective response to alcohol may be due to a direct pharmacological interaction. In contrast to LSD, the use of psilocybic mushrooms failed to fully antagonize the subjective effects of alcohol. Although nine of the 15 psilocybin users reported a diminished response to alcohol, no participants reported that the administration of psilocybin completely blocked the subjective effects of alcohol. Of the remaining six participants, five reported that psilocybin had no impact on their subjective response to alcohol, while the final subject stated that psilocybin actually enhanced the subjective effects of alcohol (i.e. caused an increase in the subjective sense of intoxication). Thus, although some participants reported a tendency for psilocybin to weaken the subjective effects of alcohol, this effect was not as pronounced as that associated with LSD; while 100 per cent of LSD users reported at least partially diminished alcohol effects, a full 40 per cent of psilocybin users failed to report any antagonizing effect. Because very little is known about the pharmacological actions of psilocybin, and the precise nature of the interaction between psilocybin and alcohol was not clearly revealed by the present data, the remainder of the discussion will focus primarily on findings concerning the concurrent administration of LSD and alcohol.

Prior to commencing a discussion of hypothesized means by which LSD could attenuate subjective alcohol effects, it would seem appropriate to address some possible limitations of the present study. The first issue concerns whether or not study participants could reliably recount their experiences with the concurrent use of alcohol and hallucinogenic drugs. There are several indications that memory is not significantly impaired by the administration of hallucinogens. For example, there are numerous reports that LSD experiences can be accurately and vividly recalled (e.g. Hofmann, 1980; Abraham *et al.*, 1996) suggesting that LSD intoxication has a negligible impact on memory storage and retrieval. The accuracy of recollections reported by subjects in the present study is further supported by the fact that most of these participants had extensive past hallucinogenic use and reported having used hallucinogens and alcohol in combination on several occasions. Thus, participants' responses to questions concerning alcohol–hallucinogen interaction effects were based on numerous experiences rather than a single event and compared to their own extensive experience with hallucinogenic drugs alone or in combination.

A second consideration concerns whether participants' recollections of alcohol effects were simply overwhelmed by the hallucinogenic properties of LSD and/or psilocybin. The observation that participants were able to reliably distinguish between LSD and psilocybin in terms of each drug's effect on the subjective alcohol experience when taken concurrently argues against this possibility. In addition, participants were highly consistent in their reporting concerning both the nature and strength of alcohol–drug interactions, despite their differential drug histories and being blind to the study's hypotheses. Finally, the amount of alcohol reportedly consumed by some participants while under the influence of LSD argues against the possibility that alcohol effects were simply overwhelmed by hallucinogen intoxication. For example, participant M described an occasion on which he had 24 drinks following the use of LSD and T recalled

drinking 18 beers, a half bottle of liqueur and 13 ounces of vodka while in a state of LSD intoxication.

While both the consistency and magnitude of reports of LSD's effect on alcohol intoxication attest to its reliability, it is important to note that in any retrospective study certain issues of potential bias may arise. Because subjects were not randomly selected it remains possible that their experiences are not characteristic of all hallucinogenic drug users. However, this possibility was minimized by the fact that participants were recruited from four different 'communities' of drug users through snowball sampling. It should also be noted that several additional steps were taken to avoid possible interviewer bias. First, questions used for queries about potential drug interactions were standardized and neutrally worded. Second, three different interviewers were used and all interviews were blindly rated. Finally, raters were instructed to eliminate cases were interviewer bias was present.

The present data are consistent with the notion that there is a direct, pharmacological interaction between LSD and alcohol. Although the current methodology did not directly examine either of these drugs' pharmacological effects, LSD is known to act at various serotonergic and dopaminergic receptor types (e.g. Peroutka, 1994; Watts *et al.*, 1995) implicated in ethanol reinforcement (e.g. Koob *et al.*, 1998) and discriminative stimulus (e.g. Kostowski and Bienkowski, 1999). This raises the possibility that LSD's effect on the subjective response to alcohol may involve an action at one or more of these systems.

LSD exerts effects at several 5-HT receptor subtypes, displaying affinity for 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-HT_{1E}, 5-HT_{2A}, 5-HT_{2C}, 5-HT_{5A}, 5-HT_{5B}, 5-HT_6, and 5-HT_7 (Peroutka, 1994; Bonson *et al.*, 1996). With respect to LSD's multiple 5-HT actions, activity at 5-HT_{2C} and/or 5-HT_{1B} receptors would seem to represent the best candidates for LSD's attenuation of subjective alcohol effects, as these are the only 5-HT receptor subtypes that have been directly implicated in the formation of the ethanol cue (Maurel *et al.*, 1998; Wilson *et al.*, 1998; Kostowski and Bienkowski, 1999). Mixed 5-$HT_{1B/2C}$ receptor agonists completely generalize to the ethanol cue in rats (Kostowski and Bienkowski, 1999; Maurel *et al.*, 1998; Szeliga and Grant, 1998), and are known to produce ethanol-like responses in humans (Kostowski and Bienkowski, 1999). Evidence also suggests that the blockade of 5-HT_{1B} and 5-HT_{2C} receptors, alone or in combination, interferes with alcohol's discriminative stimulus properties (Maurel *et al.*, 1998). In their review article, Kostowski and Bienkowski (1999) refer to such findings, and conclude that serotonergic neurotransmission plays a key role in the formation of the ethanol cue, and that this cue is primarily mediated through 5-HT_{1B} and 5-HT_{2C} receptors.

Unfortunately, the precise nature of LSD's action at 5-HT_{1B} remains unknown (Peroutka, 1994). The present discussion will therefore focus on the actions of LSD at 5-HT_{2C} receptors. LSD displays partial agonist effects at 5-HT_{2C} receptor sites (Glennon, 1990; Fiorella *et al.*, 1995; Egan *et al.*, 1998). Thus, although LSD displays high affinity, its agonist actions at 5-HT_{2C} are of low efficacy. Because LSD is a partial agonist at 5-HT_{2C} receptors, the precise nature of its effect at these sites will depend on available 5-HT concentrations and on the presence of other 5-HT agonists and/or antagonists (Glennon, 1990; see also Bonson *et al.*, 1996). At low 5-HT concentrations and/or in the absence of another agonist, LSD behaves as a low-efficacy 5-HT_{2C} agonist, achieving approximately 30 per cent maximal excitation (Marek and Aghajanian, 1996; Egan *et al.*, 1998). In the presence of a high efficacy agonist (i.e. at higher 5-HT concentrations), LSD exerts its own maximal effect while suppressing the receptor's responsiveness to the other agonist, thereby blocking the other agonist from achieving maximal excitation. Under such conditions, LSD may thus appear to function as an antagonist. LSD's partial agonist actions are consistent with the hypothesis that LSD may prevent the level of 5-HT_{2C} excitation required for the alcohol cue to be subjectively experienced, and this mechanism may underlie the findings of the present study.

The hypothesis that LSD attenuates the ethanol cue in humans through such serotonergic mechanisms is consistent with the present observation that this effect was diminished or absent following the administration of psilocybin. Although LSD and psilocybin are considered similar in terms of subjective effects, they differ with regard to serotonergic pharmacological properties. For example, LSD is known to bind to various 5-HT sites with a greater affinity than psilocybin (Glennon *et al.*, 1985; McKenna *et al.*, 1990). Furthermore, psilocybin is currently believed to act as a full agonist at 5-HT_2 receptors (Vollenweider *et al.*, 1998), whereas LSD acts as a partial agonist at these sites. If, as hypothesized, LSD exerts an effect on the alcohol cue via suppression of the requisite 5-HT_2 response, then one might expect psilocybin to fail

to fully attenuate the subjective effects of alcohol.

Aside from its actions at 5HT receptors, LSD has also been demonstrated to exert partial agonist effects at dopamine D_1 (Watts *et al.*, 1995) and D_2 (Giacomelli *et al.*, 1998) receptors. Midbrain dopaminergic activity is thought to be critical for the reinforcement of ethanol administration (e.g. Koob *et al.*, 1998). Although DA transmission is implicated in ethanol reinforcement, there is currently only limited evidence to suggest that DA transmission substantially contributes to ethanol's subjective effects. Blocking DA neurotransmission with preferential DA receptor antagonists does not appear to affect either the discriminative stimulus effects of alcohol in rats (Kostowski and Bienkowski, 1999) or the subjective effects of alcohol in humans (Litten, 1996). Although dopamine antagonists fail to significantly alter subjective ethanol effects, there is nevertheless some indication that dopamine agonists may attenuate aspects of the ethanol cue. For example, amphetamine, a potent DA receptor agonist, has been reported to antagonize ethanol effects in rats (Schechter, 1974) and cocaine administration has been shown to attenuate the sedative effects of alcohol in humans (e.g. Foltin *et al.*, 1993). Such evidence suggests that LSD's blockade of subjective alcohol effects may relate to its agonist activity at DA receptors. Unlike LSD, psilocybin does not display an affinity for DA receptors, although there is some evidence that it may increase DA transmission indirectly through serotonergic mechanisms (e.g. Vollenweider *et al.*, 1999). Nevertheless, the differential affinity of LSD and psilocybin for DA receptors may help to explain reported differences in the effects of LSD and psilocybin on the subjective response to alcohol.

In summary, the subjective effects of alcohol are antagonized by LSD and, to a lesser extent, by psilocybin. Although it is proposed that these effects may be at least partly mediated by serotonergic and/or dopaminergic mechanisms, actions at either of these systems are likely to influence a variety of physiological and neurochemical processes and the interdependence among these should not be underestimated. It should also be emphasized that the pharmacological profiles of alcohol and hallucinogens remain incompletely understood and more research is needed in order to fully understand the precise nature of the interactions among these drugs. This point is particularly relevant in the case of psilocybin, which has not been examined as extensively as either LSD or alcohol. Indeed, without a fuller characterization of each of these drugs' effects, interpretation of the present results must remain largely speculative.

Despite the fact that the present analysis is unable to fully elucidate the mechanisms governing alcohol–hallucinogen interactions, the present findings are highly relevant for several reasons. First, this is, to the best of the authors' knowledge, the first documentation of a recreational drug eliminating subjective alcohol effects in humans. Further exploration of the interaction between LSD and alcohol revealed by the present findings may ultimately enhance our understanding of the mechanisms that mediate the subjective effects of ethanol. Second, evidence suggests that alcohol is often co-administered with hallucinogenic drugs (Martin *et al.*, 1996). Given the amounts of alcohol reportedly consumed by some participants in the present study while under the influence of LSD and the illustrated potential for LSD to attenuate alcohol effects, this practice may pose significant health risks. Third, this analysis demonstrates that, despite the fact that similarity between LSD and psilocybin has been assumed by some researchers (e.g. Strassman, 1992), there is likely some discordance in the pharmacological effects of these two hallucinogens. Finally, this study illustrates a distinctive and effective approach for delineating drug–alcohol interactions in humans.

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Appendix 2:

Characteristics of methylphenidate misuse in a university student sample

Orignal Research

Characteristics of Methylphenidate Misuse in a University Student Sample

Sean P Barrett, PhD Candidate[1], Christine Darredeau, PhD Candidate[1], Lana E Bordy, BSc[2], Robert O Pihl, PhD[3]

Objective: Methylphenidate (MPH) is a prescription stimulant drug with known abuse potential; however, little is known about its patterns of misuse or the characteristics of its abusers.

Methods: A sample of 50 university students reporting MPH misuse and 50 control subjects matched for age, sex, and ethnicity completed structured face-to-face interviews about their MPH and other drug use. For each substance ever used, they provided information regarding routes of administration and other substances ever coadministered, as well as details about the most recent administration. MPH users provided additional information about their reasons for use and, in 36 cases, about how they obtained the drug.

Results: Relative to control subjects, those who misused MPH were more likely to have used various other prescription and nonprescription stimulant drugs over their lifetime, and most MPH users reported mixing the drug with other psychoactive substances. Of the MPH sample, 70% reported recreational use of the drug, while 30% reported that MPH was used exclusively for study purposes. Relative to those using it exclusively for study, recreational users were more likely to report using MPH intranasally, as well as coadministering MPH with other substances. Most of those who reported their source of MPH obtained it from an acquaintance with a prescription.

Conclusions: Those who misuse MPH are more likely than their peers to misuse various other substances, and MPH misuse frequently occurs in the context of simultaneous polydrug use. Because the primary supply of inappropriately used MPH appears to be prescribed users, efforts should be directed toward preventing its diversion.

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Clinical Implications

- MPH users reported greater lifetime use of other stimulants than did control subjects, and MPH misuse itself frequently occurred in a polysubstance use context.
- Oral MPH misuse may be more common than expected relative to other routes of administration.
- The primary source of misused MPH was identified as prescription diversion from prescribed users, suggesting that increased efforts should be directed toward ensuring prescription compliance.

Limitations

- The self-selected sample was moderately sized and may not be representative.
- Immediate- and extended-release formulations of MPH were not distinguished.
- Other reasons for MPH use in recreational users were not delineated.

Key Words: methylphenidate, prescription drug abuse, polysubstance, alcohol

Methylphenidate is a stimulant medication widely used for treating ADHD. Despite its wide margin of safety, MPH is thought to have high abuse potential (1). Cases of oral (2,3), intranasal (4,5), and intravenous (6,7) MPH abuse have been documented. However, consistent information is lacking regarding the prevalence of MPH abuse through the various routes of administration or regarding its use in a polysubstance context. Although rates of MPH abuse are thought to be lower than rates for other stimulants, it has been suggested that MPH misuse may be underreported (1). In a college student sample, rates of reported recreational MPH use among traditional-age students were comparable to rates of cocaine and amphetamine use, but any overlap in the rates of MPH and other stimulant use was not specified (8). A study

Abbreviations used in this article

ADHD	attention-deficit hyperactivity disorder
GHB	gamma hydroxybutyrate
LSD	lysergic acid diethylamide
MDMA	3,4-methylenedioxymethamphetamine
MPH	methylphenidate
PCP	phencyclidine
SD	standard deviation
SSRI	selective serotonin reuptake inhibitor

of child and adolescent MPH abuse reported to poison centres found that polysubstance use was involved in 30% of the cases overall; however, it was more common in adolescents aged 15 to 19 years than in children aged 10 to 14 years, and it was more likely to be associated with clinical toxicity (9). Although the most common route of administration was oral in both age groups, the older group was also more likely to report intranasal use (9). However, because this sample consisted exclusively of cases reported to poison centres, it may not represent general patterns of MPH misuse, and its relevance to adults who misuse MPH is unknown. In a recent study examining illicit MPH use in a university student sample, individuals who misused MPH reported using significantly more psychoactive substances during the preceding year than did peers with no history of MPH misuse (10). Although such findings suggest that individuals who inappropriately use MPH may be more prone to substance misuse in general, the context and patterns of MPH administration were not delineated, and little is currently known about how MPH is related to the use of other specific substances.

The present study aimed to elucidate patterns of MPH misuse and characteristics of MPH misusers in a university student population, including information on routes of administration, reasons for use, methods of obtaining MPH, and related patterns of past and concurrent polysubstance use.

Method

The study involved 50 individuals who reported recreational and (or) nonprescribed use of MPH and 50 control subjects matched for age, sex, and ethnicity. Participants were recruited from the McGill University student population between July 1, 2003, and May 31, 2004, as part of an ongoing study examining polydrug use in different populations. Subjects who misused MPH were recruited through advertisements posted on a university-based, classified Internet site, and control participants were recruited from a pool of volunteers who had expressed interest in participating in research at McGill's Department of Psychology. During confidential face-to-face interviews (which were standardized and structured), participants provided details about their recreational and (or) nonprescribed use of various licit and illicit substances. Participants answered questions about their lifetime use of several specific substances, including tobacco, alcohol, cannabis, LSD, psilocybin (magic mushrooms), cocaine, mescaline, methamphetamine, MPH, ketamine, GHB, MDMA (ecstasy), PCP, heroin, ephedrine, Adderall™, d-amphetamine, and "any other drug not already mentioned (please specify)." For each substance, subjects provided information regarding routes of administration and other substances ever coadministered with the drug, as well as details of all substances used simultaneously during the most recent administration. Participants were asked why they used MPH; 36 of them also indicated how they obtained the MPH. All subjects provided informed consent before participating, and all were paid $15 after their interview. The study was conducted in accordance with the Declaration of Helsinki and was approved by a McGill University research ethics committee.

Statistical Analyses

We used SPSS Version 11.0 (11) to analyze all data. We used independent sample t tests to test for differences in the total number of drugs used between subjects who misused MPH and matched control subjects, as well as between recreational MPH users and those reporting using MPH exclusively for study purposes. Chi-square tests were used to examine differences in the prevalence of the use of specific substances among these groups. Because analyses were conducted for 18 different substances, we used familywise Bonferroni corrections; the alpha level used to determine statistical significance for these tests was 0.003. Chi-square tests were also used to determine whether there were differences in the proportion of recreational MPH users and "studiers" who reported different routes of MPH administration or reported polysubstance use involving MPH.

Results

In each subject group, 46% of the participants were men and 54% were women, 86% were white (while several other ethnic backgrounds were represented, none exceeded 5% of the sample), and the mean age was 21.4 years, SD 2.6. Table 1 presents lifetime history of substance use for both subject groups. MPH misusers reported using a greater variety of substances recreationally throughout their lifetimes (mean 7.7, SD 3.0) relative to control subjects (mean 3.8, SD 3.1) (t = 5.98, df 98, $P < 0.001$). Chi-square tests revealed that MPH users were more likely to report recreational use of ecstasy, cocaine, ephedrine, d-amphetamine, and psilocybin (all Ps < 0.001) than were control subjects.

Seventy percent of those who used MPH reported using it for recreational purposes, while the remaining 30% reported

Table 1 Percentages of MPH misusers and control subjects reporting the lifetime recreational use of various licit and illicit substances

Drug type	Methylphenidate misusers	Matched control subjects	χ^2	P^a
Alcohol	100.0	94.0	3.1	0.242
Tobacco	98.0	86.0	4.9	0.059
Cannabis	96.0	76.0	8.3	0.008
Psilocybin	82.0	48.0	12.7	0.001
MDMA	78.0	24.0	19.5	0.001
Cocaine	60.0	22.0	14.9	0.001
Amphetamine	46.0	26.0	4.3	0.060
Ephedrine	42.0	2.0	23.3	0.001
LSD	30.0	20.0	1.3	0.178
Dexedrine	24.0	0.0	13.6	0.001
Adderall™	16.0	0.0	8.7	0.006
Ketamine	14.0	10.0	0.4	0.760
GHB	14.0	10.0	0.4	0.760
Sedatives	10.0	10.0	0.0	0.999
Opium or morphine	10.0	6.0	0.5	0.715
Phencyclidine	10.0	4.0	1.4	0.436
Mescaline	8.0	12.0	0.4	0.731
Heroin	6.0	6.0	0.0	0.999

[a]The Bonferroni corrected alpha level is 0.003.

using it exclusively as an aid for study. The proportion of recreational users also taking MPH as a study aid was not consistently recorded. Among the recreational users, 77.1% reported the simultaneous use of other psychoactive substances (excluding tobacco) with MPH, and 26.7% of those reporting MPH use exclusively for study purposes reported using other substances simultaneously. Chi-square analysis revealed that a greater proportion of recreational users reported using MPH in a polydrug context ($P < 0.001$). However, there were no differences between the 2 groups in lifetime number of drugs used ($t = 1.67$, df 48, $P = 0.10$) or in the proportion reporting lifetime use of any given substance (all Ps > 0.05). Table 2 presents the prevalence of using other substances concurrently with MPH, for both lifetime and most recent use, in recreational users and in those reporting use for study only, as well as in the total sample.

Overall, the most common routes of MPH administration reported were oral (88%) and intranasal (50%); other routes reported included smoking (4%) and injection (2%). When participants reported multiple administration routes, the relative frequency of each was not recorded. Among the recreational MPH users, 82.9% reported oral administration, and 62.9% reported intranasal use. In contrast, the rates of oral and intranasal use in those using MPH only for study were 100% and 20%, respectively. Chi-square analysis showed that those reporting MPH use exclusively for study were less likely to report intranasal use ($P < 0.01$); however, there were no differences in the relative proportions reporting oral administration ($P > 0.05$). Of the 36 MPH users who provided additional information about their source(s) of MPH, most (77.8%) reported obtaining it from a friend or acquaintance with a prescription. Other methods included black market purchases (16.7%), getting one's own prescription (11.1%), and theft (4%).

Discussion

In this study, we sought to elucidate characteristics of a sample of university students who misused MPH and to identify their patterns of misuse and sources of the drug. Relative to matched control subjects, the MPH users reported the recreational use of more drugs throughout their lifetime, particularly other prescription and nonprescription stimulant drugs such as cocaine, ephedrine, Adderall™, and d-amphetamine. This suggests that MPH misusers may possess a general vulnerability to stimulant misuse rather than a preference for MPH per se and that MPH may sometimes be used as substitution for more expensive or difficult-to-obtain substances, such as cocaine. It is also possible that in some cases the propensity to misuse MPH may represent an attempt to self-medicate undiagnosed ADHD symptoms (12). This may be especially true among subjects who reported nonprescribed MPH use for study purposes only. However, because these individuals reported high levels of other illicit substance use,

Table 2 Percentages of MPH misusers using the drug in a polysubstance use context

Substances used	Total MPH sample (n = 50)		Recreational users (n = 35)		Study-only users (n = 15)	
	Lifetime	Last use	Lifetime	Last use	Lifetime	Last use
Any[a]	62.0	36.0	77.1	42.9	26.7	13.3
Alcohol	50.0	24.0	71.4	34.3	0.0	0.0
Cannabis	42.0	16.0	48.6	17.1	26.7	13.3
Cocaine	10.0	0.0	14.3	0.0	0.0	0.0
Psilocybin	6.0	0.0	8.6	0.0	0.0	0.0
Sedatives	4.0	4.0	2.9	0.0	6.7	6.7
MDMA	4.0	2.0	5.7	2.9	0.0	0.0
GHB	4.0	0.0	5.7	0.0	0.0	0.0
Amphetamine	2.0	0.0	2.9	0.0	0.0	0.0
Ephedrine	2.0	0.0	2.9	0.0	0.0	0.0
Dexedrine	2.0	0.0	0.0	0.0	6.7	0.0
LSD	2.0	0.0	2.9	0.0	0.0	0.0
Tobacco[b]	na	54.0	na	54.3	na	53.3

na = not available.
[a]Excluding tobacco
[b]Lifetime prevalence data not collected for tobacco coadministration

it would be difficult to ascertain the degree to which ADHD symptoms were a cause or a consequence of their drug misuse without an adequate period of abstinence (12).

The most common route of MPH misuse in this sample was oral, and the second most common was intranasal. Oral administration was the most frequent method reported by both recreational MPH users and those using it exclusively for study, whereas intranasal use was relatively more common among recreational users. Because we did not record all the potential reasons for MPH use in recreational users or the frequency of their different administration routes, we cannot determine the relative prevalence of oral and intranasal MPH use for recreational purposes in this study. Nevertheless, our findings of oral MPH misuse are consistent with some previous reports that MPH may frequently be misused orally (1,3).

The MPH users in this study often used the drug in a polydrug context, especially with alcohol or cannabis (Table 2). Little is known about the effects of mixing MPH with other substances. Although we do not know whether the use of additional substances with MPH is associated with increased morbidity and mortality, a study of MPH overdoses in children and adolescents suggests that polysubstance use may be associated with increased toxicity (9). Alcohol–MPH coadministration is associated with the production of a novel metabolite, ethylphenidate (13), and toxic effects have been reported following the ingestion of high doses of both substances (14). There are also reports that combined alcohol–MPH administration results in enhanced euphoria and a diminished sense of drunkenness (3), which could lead to dose escalation. To our knowledge, the specific effects and consequences of the concurrent use of cannabis (or other illicit drugs) with MPH have yet to be systematically investigated. Given the high rates of drug mixing by MPH users in the present sample, further research in this area seems warranted.

Because the primary source of MPH in this sample was prescription diversion, increased attention should be directed to ensuring prescription compliance as well as to identifying those individuals most likely to divert their medication. Previous research found that adolescents who misused their own prescription stimulant medication were more likely to give it or sell it to others (15). Although it is not known whether this is also the case for adults, practitioners may wish to exert particular caution in prescribing MPH to individuals with histories of substance abuse.

Our results should be interpreted in light of several methodological limitations. First, because those who misused MPH were self-selected and the sample size was relatively modest, it is possible that the results do not represent MPH misuse in the university student population. In 2 previous studies of MPH misuse among college students, 2.5% and 16% of participants, respectively, reported inappropriate MPH use, and the respective response rates of those invited to participate were 64% and 20% (8,10). Thus obtaining a comparable number of MPH misusers by sampling an entire student population could be expected to require several thousand subjects, without any additional assurance of a representative sample. Nevertheless, only a true random sample of subjects who misuse

MPH would ensure the generalizability of the findings. Second, our investigation did not distinguish between immediate-release MPH and the newer extended-release formulation that is believed to be less liable to be abused intranasally. Although the high levels of oral MPH abuse reported may be due in part to misuse of extended-release MPH, we cannot determine the respective misuse patterns of immediate- and extended-release MPH formulations with the present data, and this issue needs to be addressed in future investigations.

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Manuscript received June 2004, revised, and accepted October 2004.
[1]Doctoral Candidate, Department of Psychology, McGill University, Montreal, Quebec.
[2]Honours Student, Department of Psychology, McGill University, Montreal, Quebec.
[3]Professor, Department of Psychology, McGill University, Montreal, Quebec.
Address for correspondence: Mr SP Barrett, Department of Psychology, McGill University, 1205 Dr Penfield Avenue, Montreal, QC H3A 1B1
e-mail: barrett@ego.psych.mcgill.ca

Résumé : Caractéristiques de l'abus de méthylphénidate dans un échantillon d'étudiants d'université

Objectif : Le méthylphénidate (MPH) est un stimulant d'ordonnance dont le potentiel d'abus est connu; cependant, on connaît peu les modèles de mauvais usage du médicament ou les caractéristiques de ceux qui en abusent.

Méthodes : Un échantillon de 50 étudiants d'université déclarant un abus de MPH et 50 sujets témoins assortis selon l'âge, le sexe et l'ethnicité ont participé à des entrevues structurées en personne, à propos de leur utilisation du MPH et d'autres drogues. Pour chaque substance déjà utilisée, ils ont fourni des renseignements sur les modes d'administration et les autres substances déjà co-administrées, ainsi que des détails sur l'administration la plus récente. Les utilisateurs de MPH ont fourni des renseignements additionnels sur les raisons de leur utilisation et, dans 36 cas, sur la façon d'obtenir le médicament.

Résultats : Relativement aux sujets témoins, ceux qui abusaient du MPH étaient plus susceptibles d'avoir utilisé d'autres stimulants d'ordonnance ou en vente libre au cours de leur vie, et la plupart des utilisateurs de MPH déclaraient mêler le médicament avec d'autres substances psychoactives. Dans l'échantillon d'utilisateurs de MPH, 70 % déclaraient un usage récréatif du médicament, tandis que 30 % déclaraient utiliser le MPH exclusivement pour étudier. Relativement à ceux qui ne l'utilisent que pour étudier, les utilisateurs récréatifs étaient plus susceptibles de déclarer un usage intranasal du MPH, ainsi qu'une co-administration avec d'autres substances. La plupart de ceux qui ont révélé leur source de MPH l'obtenaient d'une connaissance ayant une ordonnance.

Conclusions : Ceux qui abusent du MPH sont plus susceptibles que leurs pairs d'abuser de diverses autres substances, et l'abus de MPH se produit souvent dans le contexte d'utilisation simultanée de polymédicaments. Étant donné que les principaux fournisseurs de MPH illicitement utilisé semblent être des utilisateurs ayant une ordonnance, on doit tenter d'en prévenir le détournement.

Appendix 3:

Oral methylphenidate-alcohol co-abuse

Oral Methylphenidate-Alcohol Co-abuse

Editors:

The use of methylphenidate among adults diagnosed with attention deficit hyperactivity disorder (ADHD) has generated some concern.[1] Methylphenidate is considered to be a drug of high abuse potential[2] and adults with ADHD are known to have an elevated risk for substance use disorders.[3] Although methylphenidate abuse is usually thought to be restricted to intravenous and/or intranasal[4,5] modes of administration, we have recently documented several cases of oral methylphenidate abuse when it is used concomitantly with alcohol. The practice of alcohol-methylphenidate co-administration is an issue that warrants increased attention. Evidence suggests that methylphenidate is sometimes prescribed to adults with comorbid alcohol problems[3] and methylphenidate-alcohol coadministration has recently been demonstrated to result in the production of ethylphenidate,[6] a metabolite of unknown toxicity.[7]

Poly-drug users with a reported history of concomitant methylphenidate-alcohol use completed structured interviews about their experiences using these drugs in combination. These participants were recruited from the community using the snowball method of sampling, a technique that requires the researcher to make an initial set of contacts with members from a target population and to ask these contacts to introduce him/her to other potential participants.[8] In the present study, three contacts whose drug histories were known a-priori were used to recruit participants. Of the 25 individuals contacted, eight declined to participate, leaving a final sample of 17. The methods used for this investigation received ethical approval from the Department of Psychology Research Ethics Committee at McGill University. Fifteen male and two female, non-treatment seeking individuals were interviewed for study.

Participants ranged in age from 20 to 31 years (mean= 26.2; sd=3.3). All cases reported the concurrent use of these drugs on at least 10 separate occasions (range= 10–100; mean=30.5; sd=22). In each case, it was reported that the methylphenidate dose (range = 10–75 mg; mean=41.5; sd=19.5) was typically consumed in several small doses throughout the course of a drinking session. In 16 (94%) of these the primary route of methylphenidate administration was oral, while in the remaining case methylphenidate was usually consumed intranasally. Interestingly, only 12% of the cases reported that they had a prescription for methylphenidate, indicating that the vast majority obtained it illicitly. In every case, an alteration in psychotropic effects was cited as the primary reason for coadministration. Combined methylphenidate-alcohol use was described as producing a desirable effect characterized by increased euphoria and energy as well as a diminished sense of drunkenness. Four cases likened the experience to using alcohol with 'low grade cocaine' and 2 of these referred to the combination as 'diet coke'. This is particularly interesting considering that alcohol is also known to be commonly co-abused with cocaine[9] and methamphetamine,[10] drugs that share a similar pharmacological profile with methylphenidate,[11] raising the possibility that a common mechanism may mediate each of their propensities to be coadministered alcohol. In addition to desirable subjective effects a minority of cases also reported occasionally experiencing unpleasant side effects: 3 cases reported increased nausea, 2 cases insomnia, and 1 case 'jaw clenching'.

Methylphenidate-alcohol co-abuse in humans warrants further investigation. Evidence suggests that co-administration of alcohol with other psychostimulants such as cocaine[9] and methamphetamine[10] often leads to increased morbidity and mortality. Although it remains unknown the degree to which this is the case for methylphenidate, evidence suggests that the co-administration of high doses of methylphenidate and alcohol may produce toxic effects.[4]. In addition, because methylphenidate has become increasingly available to adult populations through licit[3] and illicit[12] means, alcohol-methylphenidate coadministration may become an issue of growing clinical concern. Practitioners may wish to exert caution when prescribing methylphenidate to individuals prone to alcohol abuse as well as provide explicit warnings to patients not to consume alcohol while using this prescription medication.

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SEAN P. BARRETT, BA
ROBERT O. PIHL, PHD
Department of Psychology
McGill University
Montreal, Quebec, Canada

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Appendix 4:

Heightened heart rate response to alcohol intoxication is associated with a reward seeking profile

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ALCOHOLISM: CLINICAL AND EXPERIMENTAL RESEARCH

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Heightened Heart Rate Response to Alcohol Intoxication Is Associated With a Reward-Seeking Personality Profile

Caroline Brunelle, Jean-Marc Assaad, Sean P. Barrett, Cesar Ávila, Patricia J. Conrod, Richard E. Tremblay, and Robert O. Pihl

Background: The psychomotor stimulant theory of addiction posits that sensitivity to the positively rewarding properties of alcohol puts certain individuals at higher risk for alcohol abuse. A valid and reliable index of overactivation in the reward system has been a heightened baseline heart rate (HR) increase on the ascending limb of the blood alcohol curve. The main goal of this study was to investigate the relationship between this HR response and a questionnaire measuring sensitivity to reward and sensitivity to punishment. Additional goals included looking at (1) the association between a high HR response and various personality traits (hopelessness/introversion, anxiety sensitivity, impulsivity, and sensation-seeking) and (2) the relationship between these personality traits and stimulant use.

Methods: A total of 18 low- and 19 high-HR responders completed the Sensitivity to Punishment and Sensitivity to Reward Questionnaire (SPSRQ), the Substance Use Risk Profile Scale (SURPS), and a modified version of the Addiction Severity Index.

Results: High-HR responders obtained significantly higher scores than low-HR responders on the sensitivity to reward scale of the SPSRQ, as well as increased sensation-seeking scores on the SURPS. High-HR responders were not at significantly higher risk of having used stimulants, but stimulant use was associated with higher impulsivity scores on the SURPS.

Conclusions: Novelty/sensation-seeking is among the personality traits that have been linked to heavy alcohol use. This study suggests that reward sensitivity might mediate the relationship between this personality profile and drinking behavior.

Key Words: Alcohol, Heart Rate, Behavioral Activation System, Personality Traits, Stimulant Drugs.

ALCOHOL DEPENDENCE IS one of the most prevalent psychiatric disorders (Kessler et al., 1994), yet individuals are not at equal risk of developing alcoholism. It is known that sons of alcoholics are at significantly higher risk for problematic alcohol use (Schuckit and Smith, 1996; Sher et al., 1991; Sigvardsson et al., 1996). The study of individuals genetically vulnerable to alcohol dependence has led to the identification of various neurobiological characteristics that are beginning to elucidate potential etiological pathways to alcoholism (Hill et al., 1998; Peterson et al., 1993; Porjesz et al., 1998). One of these markers, an increased heart rate (HR) response after alcohol intoxication, has been suggested as partially mediating the genetic predisposition to alcohol dependence (Conrod et al., 1998).

Some alcoholics and men at risk for alcoholism display an exaggerated HR increase after ingesting an intoxicating dose of alcohol (Conrod et al., 2001; Wilson and Nagoshi, 1988), a response noticeable only on the ascending limb of the blood alcohol curve (AL-BAC). Indeed, men with multigenerational histories of alcoholism have significantly higher HR increases on the AL-BAC than family history–negative individuals, but there are no differences in HR between the groups on the descending limb (Conrod et al., 1997). This finding may be explained by the fact that stimulant effects of alcohol seem to be solely expressed on the AL-BAC (Friedman et al., 1980; Holdstock et al., 2000; Martin and Earleywine, 1990). It has been suggested that an exaggerated HR increase on the AL-BAC reflects activation of the behavioral activation system (BAS), a system that responds to signals of appetitive cues and reward by increasing approach behaviors and positive mood (Fowles, 1980, 1983; Fowles et al., 1982; Gray, 1987). Stimulants, as well as alcohol, are thought to activate this system by

From the Department of Psychology, McGill University, Montréal, Québec, Canada (CB, SPB, ROP); Research Unit on Children's Psycho-Social Maladjustment, University of Montréal, Montréal, Québec, Canada (J-MA, RET); Department of Psychology, University Jaume I, Castelló, Spain (CÁ); and King's College, London, U.K. (PJC).

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Reprint requests: Caroline Brunelle, Department of Psychology, McGill University, 1205 Docteur Penfield, Montréal, Québec, H3A 1B1, Canada; Fax: 514-398-4896; E-mail: brunelle@ego.psych.mcgill.ca.

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potentiating the availability of neurotransmitters associated with reward, such as dopamine (DA) (Di Chiara et al., 1992; Gianoulakis, 1996; Koob et al., 1998). Haloperidol, a DA D2/D3 receptor antagonist, reduced the stimulant effects of alcohol in subjects who reported increased stimulation after alcohol ingestion compared with those who reported none (Enggasser and de Wit, 2001). Recently, it was found in a human positron emission tomography study that alcohol reduced the raclopride binding potential, indicating DA release in response to alcohol administration (Boileau et al., 2003). Moreover, this was correlated with alcohol-induced increases in HR on the AL-BAC, suggesting that alcohol-induced cardiac reactivity may be a marker of the DA-mediated reinforcing effects of alcohol. Individuals who experience more stimulating effects from alcohol on the AL seem to drink more heavily and may be at a higher risk for developing alcohol problems (Holdstock et al., 2000; King et al., 2002).

Individuals who display a heightened HR response to alcohol on the AL-BAC also tend to show a specific personality profile characterized by high extraversion, novelty/sensation-seeking (SS), and disinhibition (Assaad 2002), traits that have been described as reflecting interest in exploratory behavior. Interestingly, animal and human studies have demonstrated that those with a high interest in exploring their environment tend to be more sensitive to drug-induced reward and to use more alcohol and stimulant drugs (Dellu et al., 1996; Hooks and Kalivas, 1994; Sher et al., 2000; Zuckerman and Kuhlman, 2000). Heightened HR has been associated with a higher risk for a variety of addictive and disinhibited behaviors, such as alcoholism (Peterson et al., 1996), aggression (Assaad et al., 2003), and gambling (Brunelle et al., 2003). The previously reviewed findings offer ample support to the recent description of exaggerated HR on the AL-BAC increase as a reliable and valid index of sensitivity to alcohol-induced reward (Conrod et al., 2001).

However, increases in autonomic arousal may not only reflect input from BAS-related systems. The behavioral inhibition system (BIS; Gray and McNaughton, 2000) is a system that responds to punishment, novelty, and nonreward. When it is activated, it produces inhibition of ongoing behavior, as well as increases in arousal, attention, and anxiety. Therefore, activation of the BIS may result in increased physiologic reactivity. Alcohol has been found to possess anxiety-dampening properties through activation of the inhibitory GABAergic system (Lewis, 1996; Pihl and Peterson, 1995). Accumulated evidence seems to suggest that ethanol-induced HR reactivity on the AL-BAC is mediated solely by the BAS. Gray (1991) describes activation of the BAS as related to "emotional states of pleasurable anticipation" and compares it to a drug-induced high. As such, in high-HR responders, alcohol intoxication is correlated with feelings of energy and vigor but is unrelated to the anxiety-dampening properties of alcohol (Conrod et al., 2001). It is also associated with increased motoric reactivity (Conrod et al., 1995) and predicts potentiated memory for elating but not depressing statements (Bruce et al., 1999), characteristics that are all theoretically associated with BAS activation.

Nevertheless, although high-HR responders are believed to be oversensitive to rewards, this may be the result of reduced BIS activity rather than an overactive BAS. Reduced functioning of the BIS could make some individuals more sensitive to approaching potentially rewarding stimuli because they would no longer be under the inhibiting influence of threat. As such, it has been found that low BIS activation is related to an ability to associate punitive events with delayed rewards on a counterconditioning computer task (Ávila et al., 1999). Therefore, the first goal of this study was to investigate the relationship between a heightened HR response to alcohol and BAS/BIS activation.

The previously reviewed literature suggests that a high HR response to alcohol intoxication on the AL-BAC reflects sensitivity to the positively reinforcing properties of alcohol. Recently, an instrument was developed to measure personality and motivational risk factors for substance use (Woicik and Conrod, The Substance Use Profile scale (SURPS): an instrument for measuring personality risk for substance abuse, submitted), which included the traits of hopelessness/introversion (H/I), anxiety sensitivity (AS), impulsivity (IMP), and SS. Whereas the researchers found that H/I and AS were associated with negative reinforcement motives for alcohol and drug use, SS was related to positive reinforcement sensitivity. IMP did not seem specifically related to any particular motive for abuse, except that it seemed to be characterized by a disorganized and severe pattern of drug use. Interestingly, the study found that personality profiles suggested differential drug sensitivity. For example, an impulsive profile was related to stimulant drug dependence, whereas an SS profile seemed to indicate an increased risk for alcohol abuse. An investigation into the relationship between this instrument and heightened HR response may help to confirm that a high HR response occurs in individuals with a personality profile associated with reward sensitivity, and considering the association between these personality traits and stimulant use could offer partial confirmation to the differential drug sensitivity theory.

The main goal of this study was to study the association between an ethanol-induced HR increase on the AL-BAC and sensitivity to reward (SR)/sensitivity to punishment (SP) by using a questionnaire that respectively measures BAS and BIS activation. An additional goal was to confirm that the relationship between a high HR response to alcohol intoxication and various personality traits (H/I, AS, IMP, and SS) is theoretically in accordance with positive reinforcement motives for abuse. Finally, the relationship between these personality traits and stimulant use will be examined to replicate the results of Woicik and Conrod (The Substance Use Profile scale (SURPS): an instrument for measuring personality risk for substance abuse, submit-

ted). Specifically, given the previously reviewed findings, it was hypothesized that a high HR response to alcohol intoxication would be related to higher SR scores and would be unrelated to SP. Moreover, it was expected that SS and IMP scores would be increased in high-HR responders and that IMP would be associated with stimulant use.

METHODS

Participants

The participants were part of a longitudinal cohort of 1037 men that have been followed up since kindergarten in low socioeconomic areas of Montréal, Canada (Tremblay et al., 1994). All participants were French-speaking Caucasian men of low socioeconomic status, to control for cultural and social factors. A subsample of 177 were invited to the laboratory at the age of 13 to 14 years, where the relationship between cognitive functioning and the stability of aggressive behaviors was studied [an extensive description of this subsample is provided by Séguin et al. (1995)]. A total of 66 of these 177 individuals agreed to participate in an alcohol challenge study when they were at least 18 years of age (mean, 19.15 years; SD, 0.36 years), which is the legal drinking age in Québec. This subsample of 66 participants was not significantly different from the entire longitudinal cohort on measures of verbal intelligence, childhood family income, or self-reported delinquency over a number of years. The 66 participants were divided into 3 equal groups of 22, based on a tripartite split of the distribution of the percentage in HR change after alcohol administration. Between 50 and 62 months after the alcohol challenge, the groups of high- (n = 22) and low-HR responders (n = 22) were asked to participate in a telephone interview in which personality and stimulant use were assessed. A total of 37 participants took part in the phone interview. One participant refused, one had died since the alcohol challenge, and the remaining five were impossible to either retrace or reach by telephone. A total of 19 high-HR responders and 18 low-HR responders successfully completed the telephone interview.

Materials

Physiologic Apparatus. HR was measured with a Contact Precision, Cambridge, MA polygraph via two electrodes placed bilaterally on the chest and one on the lower left abdomen of each participant.

Alcohol Challenge. Participants consumed 1 ml of 95% alcohol USP per kilogram of body weight, which is equivalent to 0.75 g of ethanol per kilogram of body weight. The alcohol dose was presented in the form of three separate glasses containing a 1 part ethanol:6 parts orange juice solution. Participants were instructed to empty each glass in exactly 5 min to ensure a constant rate of ingestion. All participants complied with these instructions. Blood alcohol concentrations were determined by using an Alco-Sensor III (Thomas Electronic Security, Montréal, Canada), which has a measurement error of ±0.003.

Subjective Effects of Alcohol Intoxication. Subjective effects after alcohol intoxication were measured with a modified version (Schuckit et al., 1997) of the 15-item Subjective High Assessment Scale (SHAS; Judd et al., 1977). The following subscales were derived from this measure: (1) subjective effects subscale, including the first 13 items of the SHAS; (2) global negative feeling (item 14 of the SHAS: "Globally the worst I have ever felt"); and (3) global positive feeling (item 15 of the SHAS: "Globally, the best I have ever felt"). Items 14 and 15 were analyzed separately on the basis of the suggestion that they should not be included in the total SHAS score because they related to separate alcohol effect dimensions (Conrod et al., 2001).

Personality and Drug Use Assessment (Telephone Interview). The Sensitivity to Punishment and Sensitivity to Reward Questionnaire (SPSRQ; Caseras et al., 2003; Torrubia et al., 2001), the Substance Use Risk Profile Scale (SURPS; Woicik and Conrod, The Substance Use Profile scale (SURPS): an instrument for measuring personality risk for substance abuse, submitted), and the Addiction Severity Index (McLellan et al., 1980) were administered during a telephone interview.

The SPSRQ is composed of the SP and the SR subscales, which each contain 24 items. It was designed to measure the respective level of functioning of the BIS and the BAS. On the basis of a review of Gray's model, the authors of the SPSRQ suggested that to adequately measure Gray's dimensions, the BAS should correlate positively with extraversion and neuroticism, whereas the BIS should correlate positively with neuroticism and negatively with extraversion on the Eysenck Personality Questionnaire (Eysenck and Eysenck, 1975). These hypotheses were supported, because SR was related positively to extraversion (r = 0.37; $p < 0.01$) and neuroticism (r = 0.25; $p < 0.01$) and SP was associated negatively with extraversion (r = −0.48; $p < 0.01$) and positively with neuroticism (r = 0.53; $p < 0.01$). Recently, this same group of researchers (Caseras et al., 2003) compared a variety of anxiety and IMP measures to determine which were best suited to measure individual differences in BIS/BAS functioning. In addition to providing convergent and discriminant validity information on the SPSRQ, the authors also performed a factor analysis with all scales. A two-factor solution emerged that included all BIS-related scales on factor 1, whereas the second factor included almost all BAS scales. Because the SP and the SR subscales were respectively among the highest-loading scales on factor 1 and factor 2 and showed a pattern of correlations with the Eysenck Personality Questionnaire that was consistent with Gray's expectations, the authors concluded that the SPSRQ was among the best measures of Gray's BIS and BAS dimensions. Additional construct validity was obtained by using the SPSRQ scale to test predictions based on Gray's model in laboratory settings (Ávila et al.,1999; Ávila and Parcet, 2000, 2001, 2002). Finally, internal consistency and test-retest reliability seemed satisfactory for both the SP and SR subscales (α = 0.83 and 0.77, respectively; r at 1-year interval of 0.74 and 0.69).

The SURPS* is a 28-item instrument that measures the following dimensions: H/I, AS, IMP, and SS. The items were derived from a larger item pool constituting a variety of personality tests that tap into these four personality dimensions. The α coefficients ranged from 0.68 to 0.87. Test-retest reliability (mean, 39.6 days; SD, 18.75 days) was high for the H/I, IMP, and SS subscales (r = 0.74, 0.76, and 0.86, respectively) but was lower for AS (r = 0.53). Convergent and discriminant validity information was obtained by correlating the SURPS with the following personality measures: Beck Hopelessness Scale (Beck et al., 1974), Anxiety Sensitivity Index (Peterson and Reiss, 1992), Impulsiveness and Empathy Scale (Eysenck et al., 1985), Sensation Seeking Scale (Zuckerman et al., 1978), and NEO Five-Factor Inventory (NEO-FFI; Costa and McCrae, 1992). The SURPS subscales were shown to correlate best with the expected personality measures. For example, the H/I subscale was positively associated with the Beck Hopelessness Scale (r = 0.74; $p < 0.001$), with neuroticism on the NEO-FFI (r = 0.54; $p < 0.001$), and, to a much lesser degree, with the Anxiety Sensitivity Index (r = 0.26; $p < 0.001$). The H/I subscale of the SURPS also correlated negatively with extraversion (r = −0.45; $p < 0.001$) and conscientiousness (r = −0.38; $p < 0.001$) on the NEO-FFI. H/I was not significantly related to the Impulsiveness and Empathy Scale, the Sensation Seeking Scale, or the openness and agreeableness dimensions of the NEO-FFI. All SURPS subscales were shown to correspond differentially to the type of drugs abused (AS with anxiolytics/sedatives, IMP with stimulants, SS with alcohol, and H/I with opioids) and to reinforcement-specific motives of alcohol and drug use (H/I and AS with negative reinforcement motives, SS with positive reinforcement motives, and IMP with a disorganized pattern of motives). Confirmatory factor analyses confirmed that the SURPS' four-factor structure provided a better fit to the data than a two-factor model (positive versus negative reinforcement sensitivity) or a five-factor model (NEO-FFI).

An abbreviated version of the Addiction Severity Index was used to

Additional information regarding the psychometric properties of the SURPS may be obtained by corresponding with Patricia J. Woicik, Department of Psychology, State University of New York at Stony Brook, NY 11794-2500; E-mail: pwoicik@ic.sunysb.edu.

assess stimulant use. Although it is based on self-report data, this method of assessing substance use has been demonstrated to be both valid and reliable (Fals-Stewart et al., 2000).

Procedure

Alcohol Challenge. Before the alcohol challenge, individuals were contacted over the phone to determine interest in and eligibility for participation. Extensive information regarding the procedures involved in the study was provided. Criteria leading to exclusion from the study included any factor contraindicating alcohol consumption, such as self-reported medical problems or conditions; prescription drug use; illicit drug abuse or dependence; psychiatric disorders; alcohol-related offenses; or lack of familiarity with the alcohol dose required for participation in the study. In addition, participants had to be at least 18 years of age at the time of the study, which represents the legal drinking age in Québec. Participants were asked to refrain from drinking alcohol 24 hr before and from using drugs for 7 days before the day of testing. Also, they were told not to drive to and from the laboratory on the day of testing, and measures were taken to solve any transportation problems.

On the day of testing, participants were given a description of the procedures and were informed of their right to withdraw at any time, but they were told that once intoxicated, they would have to wait until their blood alcohol concentrations had reached a level less than 0.04%. Sobriety was established by breathing into the breathalyzer for 6 sec. Abstinence from drug use for 7 days before the appointment was determined by self-report. Participants were then weighed to assess the amount of alcohol to be administered and were offered a light snack before abstaining from food for the 4 hr preceding alcohol consumption. During this time, a variety of tests and tasks not relevant to this investigation were administered.

After the completion of these tasks, a sober baseline HR was obtained for all participants while they were resting comfortably in a chair. After resting for 10 min to allow adaptation to the device, the baseline sober HR was measured for 5 min, during which the participant was instructed to remain as still as possible. Alcohol was administered in the form of three glasses that were ingested at a constant rate of one drink per 5 min. Participants relaxed for 15 min to allow alcohol absorption. The SHAS was then administered to measure the subjective effects of alcohol intoxication. To ensure HR measurement on the AL-BAC (Conrod et al., 1997), each participant's intoxicated baseline HR was taken for 5 min after only 30 min after the onset of alcohol ingestion. Participants were not permitted to leave before their blood alcohol concentrations had reached a level less than 0.04%. During this time, they were invited to read or watch television and were offered a meal.

Personality and Drug Use Interview. Participants from the high- and low-HR response group were administered the SPSRQ, the SURPS, and a modified version of the Addiction Severity Index during a telephone interview that took place 50 to 62 months after the alcohol challenge. Telephone interviews have been shown to improve the quality of the data obtained when compared with face-to-face interviews (Greenfield et al., 2000; Midanik et al., 2001).

RESULTS

Data Preparation and Derivation of Cardiovascular Variables

The autonomic signals were stored in a computer for later processing. The reciprocal of the interbeat interval of the cardiac cycle was multiplied by 60,000 to obtain HR in beats per minute. Sober resting baseline HR and alcohol intoxicated resting baseline HR were calculated by averaging each respective 5-min baseline. The percentage of HR change after ethanol intoxication was obtained by subtracting the sober resting baseline HR from the intoxicated resting baseline HR and dividing the difference by the sober baseline HR. The 66 participants were divided into 3 groups, based on the distribution of percentage change in HR after alcohol intoxication. Low-HR responders included all participants in the lower third of the distribution with increases less than 9.55% (mean, 3.23%; SD, 5.75%). High-HR responders obtained HR scores in the upper third of the distribution and displayed increases more than 17% (mean, 23.50%; SD, 4.86%). The middle group of the distribution was not of interest in this study, because its main goal was to find support for a link between high and low HR response and personality characteristics. As previously mentioned, 18 of the 22 low-HR responders and 19 of the 22 high-HR responders completed the telephone interview in which personality and drug use were assessed.

All variables in the study were screened for normality and outliers. One outlier was found in the SS scores and was replaced by a score one unit larger than the next extreme score. This procedure is in accordance with Tabachnick and Fidell (1996) for when reduced sample sizes are a potential issue.

Demographics, Verbal Intelligence, and Blood Alcohol Concentrations

Separate analyses of variance were performed to determine whether high- and low-HR responders were similar on demographic variables, verbal intelligence scores, and blood alcohol concentrations. Results indicated that the differences between high- and low-HR responders on age, years of education, childhood familial income, and verbal intelligence were not significant. However, high-HR responders displayed higher blood alcohol concentrations after alcohol ingestion than low-HR responders (Table 1).

HR Response to Alcohol and the Subjective Effects of Alcohol Intoxication

No significant differences were found between high- and low-HR responders in the SHAS total (mean of items 1–13) subjective effects score [$F(1,35) = 0.009; p = 0.923$]. Because the global negative feeling subscale (item 14) was not normally distributed, nonparametric analyses were performed on this subscale. No significant differences were found in negative feelings after intoxication between high- and low-HR responders [$U(1, N = 37) = 133; p = 0.220$]. However, high-HR responders obtained significantly higher scores on the global positive feeling subscale (item 15) than low-HR responders, indicating that they experienced more positive feelings after alcohol intoxication [$F(1,35) = 5.812; p = 0.02$].

HR Response to Alcohol in Relation to the SPSRQ, the SURPS, and the Addiction Severity Index

Multiple analyses of variance were performed to determine the relationships between the HR response to alcohol intoxication and the various questionnaires administered (Table 2).

Table 1. Group Differences Between Low- and High-HR Responders to Alcohol Intoxication on Demographics, Intellectual Functioning, and Blood Alcohol Concentrations (BACs)

Baseline variables	Low responders Mean	Low responders SD	High responders Mean	High responders SD	*df*	*F*	*p* Value
Age (years)[a]	19.18	0.39	19.06	0.24	33	1.10	0.30
Years of education[b]	11.56	1.50	11.26	2.13	34	0.22	0.64
Childhood household income[c]	6.54	3.33	5.82	2.72	29	0.42	0.52
Verbal intelligence score[d]	9.22	2.02	9.44	2.09	35	0.11	0.75
BACs	0.064	0.016	0.081	0.018	31	7.89	0.01

[a] Age at time of alcohol challenge.
[b] Years of education completed at the time of alcohol challenge.
[c] Household income at age 10. Family income scale ranges from 1 to 13; 1 indicates revenues less than $5,000 (Canadian dollars), with increments of $5,000 until 13, which represents salaries more than $60,000.
[d] Verbal intelligence was assessed at age 13 by using the Sentence Completion Test (Veroff et al., 1971). Scores can range from 0 to 13 on this test.

Table 2. Group Differences Between Low- and High-HR Responders to Alcohol Intoxication on the SPSRQ, the SURPS, and the Addiction Severity Index

Variable	Low responders Mean	Low responders SD	High responders Mean	High responders SD	*df*	*F* or χ^{2a}	*p* Value
SP	6.83	3.84	7.16	4.69	36	0.05	0.82
SR	11.00	3.68	13.68	4.03	36	4.46	0.04
H/I	13.78	3.46	11.11	2.77	36	6.78	0.01
AS	14.89	2.45	14.63	4.57	36	0.05	0.83
IMP	15.22	3.00	17.26	3.78	36	3.28	0.08
SS	18.00	2.11	19.74	2.55	36	5.04	0.03
Cannabis (%)[b]	88.89		94.74		1	0.42	0.48
Cocaine	16.67		26.32		1	0.51	0.38
Amphetamine	16.67		15.79		1	0.94	0.64
Ecstasy	16.67		10.53		1	0.30	0.47

[a] Chi-square tests were performed on categorical data.
[b] Percentage of individuals that used cannabis, cocaine, amphetamine, or Ecstasy more than five times. The response was scored as 0 (no) or 1 (yes).

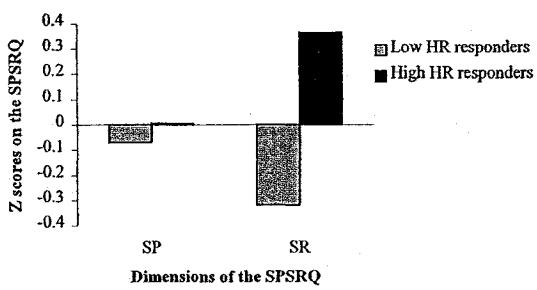

Fig. 1. Mean group differences between low-HR responders (n = 18) and high-HR responders (n = 19) on the SPSRQ.

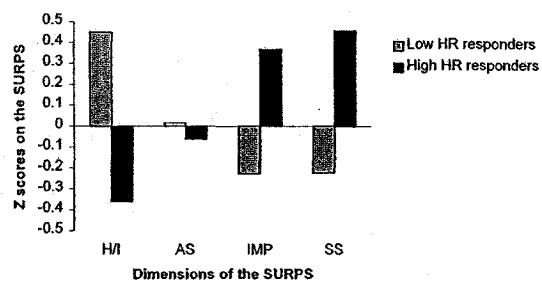

Fig. 2. Mean group differences between low-HR responders (n = 18) and high-HR responders (n = 19) on the SURPS.

On the SPSRQ, high-HR responders had significantly higher SR scores but were not significantly different from low-HR responders on SP (Fig. 1). On the SURPS, high-HR responders had significantly lower H/I and higher SS scores as compared with low-HR responders. There was also a trend for high-HR responders to obtain higher IMP scores, but no differences in AS were obtained between groups (Table 2 and Fig. 2). One-tailed χ^2 tests were performed to examine the relationship between HR response and stimulant use. No significant differences in drug use emerged between high- and low-HR responders (Table 2).

Because a significant difference in blood alcohol concentrations was found between the two HR response groups, one-tailed partial correlations controlling for blood alcohol concentrations were performed between the personality variables and HR response. Results were essentially unchanged: SR (partial $r = 0.39$; $p = 0.01$) and SS (partial $r = 0.35$; $p = 0.03$) were significantly associated with an alcohol-induced HR increase on the AL-BAC, whereas there was a trend for a positive relationship between IMP and cardiac reactivity (partial $r = 0.28$; $p = 0.06$). The negative relationship between H/I and HR response became a nonsignificant trend (partial $r = -0.29$; $p = 0.06$) when blood alcohol concentrations were controlled for.

The SURPS in Relation to the Addiction Severity Index

Participants who had used cocaine more than five times obtained significantly higher scores on the IMP dimension

of the SURPS [$F(1,36) = 5.68$; $p = 0.02$]. Those who had used amphetamines more than five times also obtained higher IMP scores [$F(1,36) = 6.98$; $p = 0.01$] on the SURPS. Individuals who had used Ecstasy more than five times had a tendency to obtain higher IMP scores, although the difference did not reach significance [$F(1,36) = 3.14$; $p = 0.09$]. No other significant relationships were found between the remaining subscales of the SURPS and stimulant use.

DISCUSSION

This study looked at the relationship between heightened HR responses to alcohol intoxication on the AL-BAC and personality. We found that high-HR responders obtained significantly higher SR scores when compared with low-HR responders. These results suggest that individuals with a heightened HR response are more sensitive to reward, which may reflect overactivation of the BAS. High-HR responders did not seem to differ from low-HR responders on the SP scale, which is thought to measure activation of the BIS.

We also found that an increased HR response to alcohol was associated with increased SS scores and positive feelings after alcohol intoxication. Many studies involving both human and animal subjects have associated SS/novelty-seeking with alcohol use (Dåderman, 1999; Fernández-Teruel et al., 2002; Galen et al., 1997; Johansson and Hansen, 2002). Recent research seems to indicate that the mechanism through which this personality profile and drinking may be related involves the dopaminergic system. Leyton et al. (2002) found that individuals high in novelty-seeking had greater amphetamine-induced DA release and responded to the drug challenge by desiring more of the drug. Similarly, rats high in exploratory behaviors drink more ethanol and show increased ethanol-induced DA activation and enhanced place preference for ethanol (Fernández-Teruel et al., 2002). It has also been found that high SS predicts drinking for its capacity to increase positive affect (Comeau et al., 2001). The previously reviewed evidence suggests that reward sensitivity might mediate the relationship between this personality profile and drinking behavior. Therefore, the possibility that a high HR response may be a neurobiological marker for a pathway that leads to alcohol problems through seeking highly pleasurable experiences should be further investigated.

We had hypothesized that high-HR responders would obtain higher IMP scores than low-HR responders on the SURPS. Although we observed a trend in this direction, the difference between groups was not significant. It is possible that with a larger sample size, the hypothesis would have been confirmed. However, some evidence suggests that SS and IMP might be risk factors that underlie separate etiological mechanisms. Finn et al. (2000) found that social deviance and excitement/pleasure-seeking were two separate biopsychosocial pathways that led to alcohol problems in individuals with a family history of alcoholism. The former includes self-regulatory deficits and lack of consideration for social norms and may involve frontal region or septohippocampal deficits. The excitement-seeking pathway was described as involving SS traits that were associated with BAS functioning, sensitivity to pleasurable activities, and mesolimbic DA influences. Furthermore, it has been suggested that these two separate pathways have independent genetic influences (Mustanski et al., 2003). Sensation-seekers seem to drink to benefit from ethanol's positively reinforcing qualities, as demonstrated in studies involving both adults (Conrod et al., Anxiety sensitivity, introversion/hopelessness, sensation seeking and impulsivity: different patterns of reinforcement sensitivity and drug abuse susceptibility, unpublished data) and adolescents (Comeau et al., 2001). IMP seems not to be associated with specific motives as such, except for a disorganized and severe pattern of drug abuse (Woicik and Conrod, The Substance Use Profile scale (SURPS): an instrument for measuring personality risk for substance abuse, submitted). Moreover, an impulsive profile was found to co-occur with antisocial personality disorder, whereas SS did not (Conrod et al., 2000). It is thought that IMP is associated with vulnerability to alcoholism through a pathway that includes antisocial personality disorder and deficits in executive cognitive function (Finn et al., 2002). Therefore, preliminary evidence suggests that a high HR response on the AL-BAC may be more closely related to the risk factor of SS than IMP.

An additional goal was to investigate HR response and personality traits in relation to stimulant use. It was found that high-HR responders did not use stimulants significantly more often than low-HR responders but that stimulant users had higher IMP scores. Our findings are similar to those of another study that found IMP, but not SS, to be associated with stimulant use (Conrod et al., 2000). This may offer additional support to the idea that IMP and SS are associated with distinct motivational reasons for abuse, as well as with different drug use patterns.

This study expands our understanding of the relationship between personality and drinking behavior. A high-HR response seemed to be associated with a reward-seeking personality profile, as demonstrated by increased SR and SS scores. This study and others suggest that further work is needed to fully disentangle the different mechanisms that underlie the personality risk for alcoholism. Work in this area may have been impeded by using broad terminology that may obscure distinct mechanisms of etiological risk (Finn et al., 2000). Additional research might focus on finding characteristics that separate sensation-seekers from impulsive individuals. Moreover, to further expand on the differential sensitivity theory, the question of whether increased scores on the SP scale (reflecting BIS activation) could indicate negative reinforcement motives of abuse should be investigated. This may be possible because anxiety is associated with using alcohol for its capacity to

reduce negative affective states (Stewart et al., 1997) and because BIS activation represents individual vulnerability to anxiety (Torrubia et al., 2001).

There are, nevertheless, limitations to our study. A small homogenous sample composed of young French-speaking men from a low socioeconomic status Canadian neighborhood limits the generalizability of the findings to other populations. Furthermore, no placebo control group was included in the study. No differences seem to occur in HR responses to placebo in subjects with or without a family history of alcoholism (Newlin and Thomson, 1999), suggesting the lack of expectancy effects in the alcohol-HR relationship. Finally, although our results may suggest that a heightened HR response to alcohol intoxication is associated with a pathway that leads to alcohol problems through reward-seeking personality traits, the study design does not allow us to conclude that this is indeed the case. A prospective study will be necessary to offer more support to the idea that the HR response to alcohol mediates the relationship between personality and alcohol problems.

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Appendix 5:

The hedonic response to cigarette smoking is proportional to dopamine release in the human striatum as measured by positron emission tomography and [^{11}C] raclopride

The Hedonic Response to Cigarette Smoking Is Proportional to Dopamine Release in the Human Striatum as Measured by Positron Emission Tomography and [^{11}C]Raclopride

SEAN P. BARRETT,[1,2] ISABELLE BOILEAU,[1] JOHANNA OKKER,[1] ROBERT O. PIHL,[2] AND ALAIN DAGHER[1]*

[1]*McConnell Brain Imaging Centre, Montreal Neurological Institute, Montreal, Canada*

[2]*Department of Psychology, McGill University, Montreal, Canada*

KEY WORDS addiction; nicotine; basal ganglia; caudate; tobacco

ABSTRACT Positron emission tomography and [^{11}C]raclopride were used to assess the dopaminergic response to cigarette smoking in ten smokers. Nicotine-deprived smokers were scanned twice on separate days. In one condition, participants smoked their usual brand of cigarettes while in the scanner and in the other condition they remained nicotine abstinent. On each day, subjects monitored the hedonic properties of their experience as well as their levels of craving. Initial analyses revealed no significant differences between the conditions in [^{11}C]raclopride binding potential (BP) in the caudate, putamen, or ventral striatum. Because previous research suggested that drug-induced dopamine transmission is related to levels of craving and/or hedonic drug effects, the relationship between these variables and [^{11}C]raclopride BP was examined. Craving levels were reduced by smoking but were not systematically related to BP change. However, the hedonic response to smoking was correlated with BP reduction in the caudate ($P < 0.001$) and posterior putamen ($P < 0.05$) but not in the ventral striatum. Post hoc analyses revealed that only five of the ten smokers reported mood-elevating effects in response to the smoking procedure. In these subjects, smoking was associated with decreased [^{11}C]raclopride BP in the caudate. On the other hand, among subjects that reported a diminished mood response to smoking there was an increase in BP in the caudate and putamen. These results suggest that pleasurable drug experiences are associated with increased dopamine transmission in the dorsal striatum while unpleasant experiences may be related to decreased dopamine release in this region. **Synapse 54:65–71, 2004.**

INTRODUCTION

Cigarette smoking has been identified as the leading cause of preventable death in industrialized nations (Polin, 1984). While cigarette smoke contains several thousand compounds (Schmeltz and Hoffmann, 1976), tobacco dependence appears to be predominantly associated with the addictive properties of a solitary alkaloid, nicotine (e.g., Domino, 1998). Evidence in rodents suggests that important aspects of nicotine addiction may be mediated by central dopamine (DA) systems. For example, nicotine administration leads to increased DA cell firing in the ventral tegmental area (Corrigall et al., 1994) and increased DA release in the nucleus accumbens (Pontieri et al., 1996), actions thought to be critical to the reinforcing properties of several addictive substances (Wise 1996; Di Chiara and Imperato 1988). In addition, disruption of DA function in rats has been shown to attenuate nicotine self-administration (Corrigall et al., 1994), nicotine-induced locomotor stimulation (Clarke et al., 1988), as well as the acquisition of nicotine-related place preference (Di Chiara, 2000). Despite evidence linking nicotine's ad-

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*Correspondence to: Alain Dagher, MD, Montreal Neurological Institute, 3801 University St., Montreal QC, Canada H3A 2B4. E-mail: alain@bic.mni.mcgill.ca

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dictive properties with its central DA actions, nicotine's DA stimulating properties are relatively weak compared to other addictive substances such as amphetamine or cocaine (Yanagita et al., 1995; Tsukada et al., 2002; Marenco et al., 2004; see Cumming et al., 2003) and appear more akin to those produced by "natural" reinforcers such as food (Di Charia, 2000). Evidence linking nicotine administration to DA release in humans and in non-human primates is currently limited. In a PET study using anesthetized baboons, intravenous nicotine reduced the mean distribution volume ratio of the D2 tracer [^{11}C]raclopride, an action thought to reflect increased DA release (Dewey et al., 1999). While similar results have been reported in anesthetized pigs (Cumming et al., 2003) and anesthetized rhesus monkeys (Marenco et al., 2004) these findings have not been consistently replicated in fully conscious monkeys (Tsukada et al., 2002) and it is possible that the initial findings resulted from an interaction between nicotine and isoflurane anesthesia (Tsukada et al., 2002). In a functional magnetic resonance imaging study in humans, smokers that passively received intravenous nicotine displayed an increase in the blood oxygen level dependent signal in several DA rich regions including the nucleus accumbens (Stein et al., 1999). However, these findings should be interpreted with caution because the route of nicotine administration differed from that used by smokers and the methodology did not directly measure DA release.

The present investigation used PET and [^{11}C]raclopride to assess the dopaminergic response to acute cigarette smoking in humans. Experimental evidence indicates that drug-induced DA release in the striatum causes a reduction in [^{11}C]raclopride binding potential (BP) that is proportional to the increase in extracellular DA (Endres et al., 1997). Although the exact mechanism by which enhanced DA transmission leads to a reduction in [^{11}C]raclopride BP is likely more complex than what could be explained by a simple competition model (Tsukada et al., 2000), this technique has been successfully used to delineate the dopaminergic effects of several abused substances in humans, including cocaine (Schlaepfer et al., 1997), amphetamine (Drevets et al., 2001; Martinez et al., 2003; Leyton et al., 2002), methylphenidate (Volkow et al., 2003), and alcohol (Boileau et al., 2003). Previous PET data suggest that DA release in the striatum is related to various motivational and rewarding processes in humans. For example, decreased [^{11}C]raclopride BP in the ventral striatum (including the nucleus accumbens) is associated with the appetitive (Leyton et al., 2002) and euphoric (Martinez et al., 2003; Drevets et al., 2001) effects of amphetamine, while the pleasurable effects of food (Small et al., 2003) have been associated with decreased [^{11}C]raclopride BP in the dorsal striatum (caudate and putamen). Thus, a goal of this study was to examine the DA properties of nicotine craving and the hedonic effects of smoking.

METHODS

Subjects

Ten right-handed, non-medicated smokers (5 males) with a mean age of 28.1 years (SD = 9.45) were recruited from the community using word of mouth and advertisement. All were regular smokers, smoking an average of 18 (SD = 7.6) cigarettes daily for an average of 11.2 years (SD = 10.5) and all were free from current or previous neurological or mental illness, including past or present substance use disorders other than nicotine dependence. None reported use of illegal drugs in the previous 30 days and all met a minimum of two DSM IV criteria for nicotine dependence. Following a complete description of the study, all participants provided written informed consent. The study was conducted in accordance with the Declaration of Helsinki and was approved by the Research Ethics Committee of the Montreal Neurological Institute.

Procedure

Each participant was scanned twice. In one condition, subjects smoked their usual brand of cigarettes while in the scanner, and in the second condition participants did not smoke. In both conditions, participants remained abstinent from cigarettes for a minimum of 12 hours, alcohol for a minimum of 24 hours, and from food and caffeine for a minimum of 4 hours prior to their scans. All scans were performed at the same time of day (mid-afternoon) following overnight cigarette abstinence. The sequence of scans was counterbalanced across subjects to avoid order effects. Abstinence from smoking was confirmed with a breath carbon monoxide analyzer (Vitalograph Breath CO, Lenexa, KS), using a maximum cutoff of 10 parts per million. Every 15 minutes while in the scanner, subjects were asked to verbally rate the hedonic value of their experience as well as their level of craving by numerically indicating their agreement with the following statements: "I feel elated or euphoric" and "I am craving a cigarette right now" (on a scale from 1 = strongly disagree, to 10 = strongly agree).

In the smoking condition, cigarette consumption began 15 minutes prior to [^{11}C]raclopride delivery. The average nicotine yield of each cigarette smoked by the subjects ranged from 1.9–2.4 mg (mean = 2.1; SD = 0.1). Subjects were asked to smoke at a rate of one cigarette every 12 minutes to a maximum of six cigarettes. In two cases, only five cigarettes were smoked due to complaints of adverse effects. In order to avoid additional unpleasant responses, the smoking regimen was altered for the final two subjects so that only three cigarettes were smoked. In each case, smoking was carefully monitored to ensure a steady pace of smoking

as well as minimal movement in the scanner. Head position was verified throughout the scans using a laser mounted on the camera.

PET image acquisition and analysis

Dynamic PET (63 slices, 26 time frames of 60 minutes total duration) was performed using the CTI/Siemens ECAT HR+ camera with lead septa removed, with a theoretical spatial resolution of 4.2 mm full width at half maximum. A transmission scan for attenuation correction was first performed using a ^{68}Ge source. Then, [^{11}C]raclopride (10 mCi in 10 ml of saline) was injected over 120 seconds into the antecubital vein and dynamic acquisition was begun. High-resolution 1.5 T T1-weighted MRI scans were obtained at a separate time for each subject for the purpose of anatomical co-registration.

PET frames were summed and co-registered with the MRI, and both images were transformed linearly into standardized stereotaxic space using the Montreal Neurological Institute template (Collins et al., 1994). Parametric maps of [^{11}C]raclopride BP were generated using a simplified reference region method (Lammertsma and Hume, 1996; Gunn et al., 1997). Regions of interest (ROI) were drawn in a two-step process using automated followed by manual anatomical segmentation. First, each subject's MRI was automatically segmented into predefined anatomical regions using the program ANIMAL (Collins et al., 1995). Then, the ROI for caudate, putamen (divided into an anterior and posterior part by the anterior commissural line), and ventral striatum were manually revised on the co-registered MRI following the anatomical segmentation suggested by Martinez et al. (2003), which is based on the known subdivision of the striatum in primates (Parent, 1990). BP values were extracted from each ROI and corrected for partial volume effects using a method that takes into account the noise and resolution characteristics of the scanner (Aston et al., 2002). It is feasible to perform the partial volume correction on the BP images rather than on the original radioactivity images since the simplified compartmental model is linear. Finally, the segmented MRI was used to generate a 4-dimensional template that was used for head motion detection and correction, using a previously described method (Zald et al., 2004). Only five of the scans exhibited head motion greater than 2 mm (range: 2.5 to 4 mm), and these were motion-corrected.

Because previous research has linked both craving and hedonic drug-related effects to changes in [^{11}C]raclopride BP (Drevets et al., 2001; Leyton et al., 2002; Martinez et al., 2003), analyses were also performed to examine the relationship between these variables and BP change. For the two behavioral variables, baseline and overall differences between the two scans were evaluated using paired-samples t-tests, and Pearson's correlations were used to examine the relationship between the average smoking-induced change in the variable and the percent change in [^{11}C]raclopride BP for each ROI.

In addition to ROI analysis, voxelwise estimation of the change in BP was also carried out to generate statistical parametric images as previously described (Aston et al., 2000). Two types of statistical maps were generated: a subtraction between smoking and nonsmoking, and a regression map to assess the relationship of BP change to craving and hedonic measures. For the latter, a linear regression was performed at each voxel between the nicotine-induced increase in euphoria rating and the difference in [^{11}C]raclopride BP between the smoking and control scans.

RESULTS

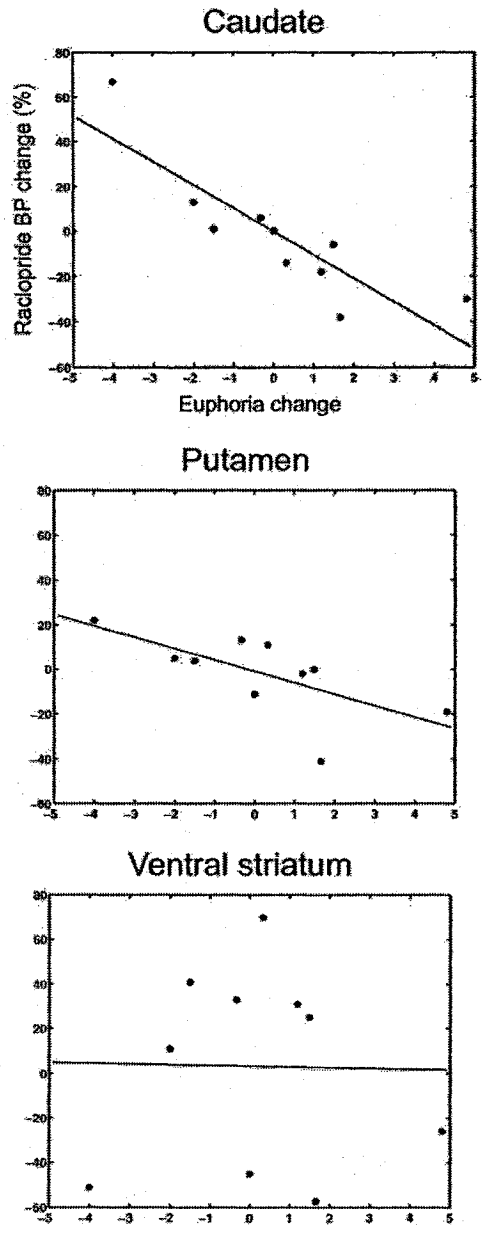
Paired samples t-tests revealed no overall significant differences in [^{11}C]raclopride BP between the smoking and control conditions in any of the ROI (all $P > 0.05$) and this was confirmed by the statistical parametric subtraction map. The mean change in BP between the smoking and abstinence scans was 3.12% for the ventral striatum, −1.9 % for the caudate, 2.9% for the anterior putamen, and −1.59% for the posterior putamen.

Smoking-induced changes in elation/euphoria were found to be significantly correlated with changes in [^{11}C]raclopride BP in the caudate ($r = -0.859$; $P < 0.001$) and posterior putamen ($r = -0.679$; $P < 0.05$), but not in the ventral striatum ($r = -0.015$; $P = 0.967$) (Fig. 1). No significant relationships between BP and smoking-induced changes in craving were revealed by correlation analysis.

In order to determine if various demographic and smoking-related variables were associated with regional smoking-induced changes in [^{11}C]raclopride BP, stepwise linear regressions were preformed using age, gender, number of cigarettes smoked daily, number of cigarettes smoked during the scan, duration of lifetime smoking, nicotine content of cigarettes, smoking-induced changes in elation/euphoria, and level of craving as potential predictor variables. In both the caudate and posterior putamen, smoking-related elation/euphoria was retained as the sole predictor of [^{11}C]raclopride BP change. No associations were found between any of the variables and change in [^{11}C]raclopride BP in the ventral striatum.

A post hoc inspection of the data revealed that in five subjects smoking produced an increase in elated/euphoric ratings, in four subjects it produced a decrease, and in the remaining subject there was no change (Table I, Fig. 2). Paired samples t-tests demonstrated that among subjects experiencing an increase in elation/euphoria in response to smoking, there was a significant 21.3% decrease in [^{11}C]raclopride BP in the caudate ($t(4) = -2.92$; $P = 0.043$) as well as a nonsignificant trend towards decreased BP in the posterior

putamen ($P > 0.05$). In those experiencing a decrease in elation/euphoria, there was a significant 11.3% increase in BP in the posterior putamen (t (3) = 3.30; $P = 0.046$) and trends toward increased BP in the caudate ($P > 0.05$) and anterior putamen ($P > 0.05$). The statistical parametric correlation map confirms the association between reduced [^{11}C]raclopride BP and euphoria (Fig. 3).



Additional analyses were preformed to determine if there were systematic differences within or between the scans in levels of craving or elation/euphoria. Craving levels prior to the start of the scan did not significantly differ between the control and smoking conditions. Craving was reduced in the experimental condition following the initiation of smoking (t (9) = −2.88; $P = 0.018$) and overall greater levels of craving were reported during the control scan (t (9) = 2.76; $P = 0.022$). There were no significant baseline or overall differences between the smoking and control scans in reported levels of elation/euphoria ($P > 0.05$).

DISCUSSION

In this study, the effects of cigarette smoking on DA neurotransmission were dependent on and proportional to the hedonic response of each subject. Participants were required to smoke multiple cigarettes lying on their backs in the scanner. For some subjects, this was an enjoyable experience while others found it unpleasant. The participants' level of enjoyment appeared to be reflected in changes in DA neurotransmission in the dorsal striatum (Fig. 2).

However, we failed to detect a purely pharmacological effect of nicotine on DA transmission. Looking at the group of subjects as a whole, there was no overall reduction in [^{11}C]raclopride BP in any subdivision of the striatum in response to acute repeated cigarette smoking. These findings suggest that the pharmacological actions of cigarette smoking may not be in and of themselves sufficient to reduce [^{11}C]raclopride BP in human smokers. Although abundant animal research suggests that various aspects of nicotine addiction are mediated by DA systems (e.g., Di Charia, 2000), the present findings are consistent with observations that, relative to other abused substances, nicotine may only have relatively weak DA actions (e.g., Yanagita et al., 1995, Marenco et al., 2004). Alternatively, our failure to observe a significant overall reduction in [^{11}C]raclopride BP may have resulted from nicotinic receptor desensitization resulting from repeated administration. In rodents, nicotine increases DA transmission through stimulation of the nicotinic receptors on DA-containing neurons (Pontieri et al., 1996) and repeated nicotine administration results in a desensitization of these receptors (Pidoplichko et al., 1997). Thus, while

Fig. 1. Relationship between euphoria and dopamine release. Plots of the percent difference in [^{11}C]raclopride BP between the smoking and non-smoking scans versus the change in self-reported euphoria after smoking. A reduction in BP indicates an increase in dopamine transmission. In the caudate nucleus and posterior putamen, there was a statistically significant correlation between euphoria and dopamine release (see text for details) but not in the ventral striatum.

TABLE I. Tobacco-induced changes in euphoria and [11c]raclopride BP for each participant[1]

Subject	Baseline euphoria	Post-smoking euphoria	Caudate (%)	Posterior putamen (%)	Anterior putamen (%)	Ventral striatum (%)
9	1	+4.8	−30	−19	−16	−26
8	3	+1.7	−38	−41	−26	−57
7	2	+1.5	−6	0	6	25
2	3	+1.2	−18	−2	16	31
10	4	+.33	−14	11	13	70
6	1	0	0	−11	−7	−45
1	2	−.33	6	13	21	33
4	3	−1.5	1	4	12	41
5	4.5	−2	13	5	6	11
3	5	−4	67	22	4	−51

Euphoria was measured using a 10-point scale (1–10). The post-smoking euphoria value represents the change from baseline. The change in [11C]raclopride BP represents the percent difference between the smoking and non-smoking scans.

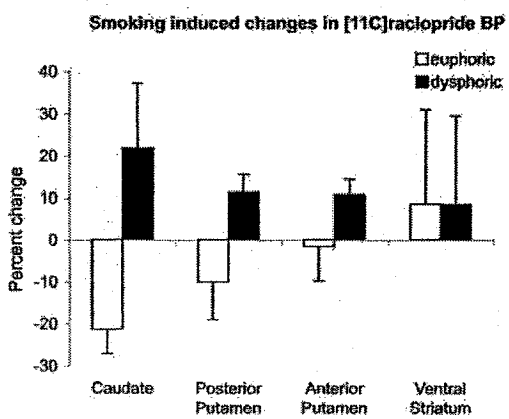


Fig. 2. Change in [11C]raclopride BP in the striatum. Subjects who experienced the smoking/PET session as pleasant demonstrated increased dopamine release in the dorsal striatum. However, subjects who experienced decreased euphoria from smoking demonstrated evidence of reduced dopamine release in all striatal areas.

an initial cigarette may stimulate DA transmission, subsequent cigarettes may not cause further DA release unless there is an adequate refractory period (Pidoplichko et al., 1997). The cigarette smoking procedure utilized in this study required participants to smoke 3–6 cigarettes in 12-minute intervals, beginning 15 minutes prior to [11C]raclopride administration. Although this smoking regimen was selected in order to maximize the nicotine response, it may have in fact resulted in desensitization, thereby reducing any nicotine-induced DA effects.

Another consideration concerns the possible effect of nicotine craving on DA transmission. Although there is currently no direct human evidence for a DA mediation of nicotine craving, animal models suggest that DA transmission in the ventral striatum mediates cravings for addictive substances that possess DA agonist actions (e.g., Robinson and Berridge, 1993; Wise, 1988). In the present study, levels of craving were not related to [11C]raclopride BP change in either the ventral or dorsal striatum. However, a ceiling effect may have been reached because all subjects were nicotine-deprived and displayed high levels of craving prior to each scan. Moreover, while craving levels significantly decreased following smoking in the experimental condition, they remained elevated throughout the control scan. Thus, if nicotine cravings are indeed associated with increased DA transmission, it is possible the persistently elevated level of craving during the control scan may have negated our ability to detect a nicotine-specific DA response in the experimental condition.

Nonetheless, a possible explanation for the absence of a detectable effect of smoking on DA release in the group as a whole may be that DA release is the result of an interaction between the pharmacological effects of nicotine and the hedonic response to the cigarette. Indeed, among those who found the smoking procedure pleasurable, there was evidence for DA release in the neostriatum, and in those who found it aversive there was decreased DA transmission in this region (Fig. 2). These findings are consistent with animal data that show increased DA cell firing in response to rewarding events but decreased DA neuronal activity in response to events that are less rewarding than expected (e.g., Schultz et al., 1997).

The relationship between DA activity and the hedonic effects of smoking was only apparent in the dorsal striatum, and not in the limbic ventral striatum (Figs. 1–3). A growing body of evidence has implicated the dorsal striatum as a key site for differentiating the hedonic value of rewarding and punishing events in humans. For example, in a recent fMRI study the dorsal striatum exhibited a differential response to monetary gains and losses (Delgado et al., 2003). Similarly, Small et al. (2001) reported that the pleasurable effects of eating chocolate correlated with regional cerebral blood flow increases in the dorsal caudate and putamen but not the ventral striatum. Finally, in two recent [11C]raclopride PET studies, we showed that the pleasurable effects of eating a meal correlated with DA release in the dorsal but not ventral striatum (Small et

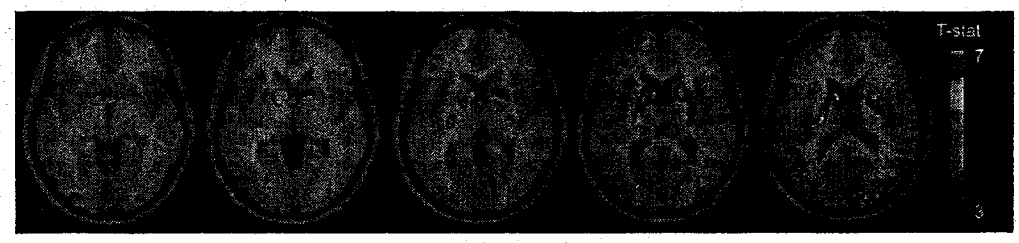


Fig. 3. Correlation between the reduction in [^{11}C]raclopride BP and euphoria. Statistical parametric map of the *t*-statistic of the linear regression of the reduction in [^{11}C]raclopride BP between smoking and non-smoking scans and the increase in euphoria resulting from smoking. The statistical map is overlaid on an average MRI image of all subjects in stereotaxic space. Axial sections from z = −5 mm to z = +15 mm at 5-mm intervals are shown (relative to the anterior commissure). The correlation is greatest in the dorsal and posterior parts of the neostriatum. The left side of each image represents the left side of the brain.

al., 2003), and that monetary reward led to DA release in dorsal parts of the striatum (Zald et al., 2004). Human drug administration studies have produced less consistent results. The euphoric effects of amphetamine have been reported to correlate with the level of DA release in the ventral striatum (Drevets et al., 2001; Martinez et al., 2003) but this finding has not been consistently reported (Leyton et al., 2002). It should be noted, however, that while the present investigation examined the effects of tobacco self-administration in nicotine-dependent smokers, each of the amphetamine studies cited used drug-naive participants who passively received the drug. Thus, disparities in the expression of hedonic drug effects between studies may reflect differences in the type of drug administered, the route and method of administration, or the previous drug-taking experiences of the participants. For example, there is evidence that expectation of a positive drug effect in humans is associated with DA release in the striatum (de la Fuente-Fernandez et al., 2001).

The present results should be interpreted in light of the following considerations. First, while participants were permitted to smoke their usual brand of cigarettes during the scan, the experimenters determined the frequency and rate of cigarette administration and this likely affected their hedonic value. An alternative design where participants were permitted to smoke ad lib might provide a superior index of how cigarette smoking affects DA transmission under "typical" smoking conditions. Second, variability in nicotine concentrations of the different brands of cigarettes smoked as well as potential individual differences in nicotine metabolism may have led to differences in plasma nicotine concentrations. Although plasma nicotine levels were not directly measured in this study, this is an unlikely explanation for our findings. Numerous cigarette-smoking parameters were found to be unassociated with changes in [^{11}C]raclopride binding including nicotine content of the cigarettes smoked, number of cigarettes smoked during the scan, and daily cigarette consumption, suggesting that the effect of differences in plasma nicotine on our results was likely minimal. Finally, the sample size in this study was modest (n = 10), but was well within the norms for assessing within subject drug effects, and the overall associations between the hedonic effects of smoking and change in [^{11}C]raclopride BP in the caudate ($P < 0.001$) and posterior putamen ($P < 0.05$) were robust. Even when participants were divided into those experiencing euphoric and dysphoric effects, the reported [^{11}C]raclopride BP changes still exceeded $P < 0.05$ and small sample size is typically associated with increased incidence of type I but not type II error.

In conclusion, although cigarette smoking failed to consistently alter DA transmission in the group as a whole, a relationship was observed between smoking-induced hedonic effects and DA release in the dorsal striatum. In subjects experiencing a positive mood response to smoking, there was evidence for increased DA release, while decreased DA activity was associated with a negative mood response.

These findings suggest that changes in DA transmission in the dorsal striatum are related to the valence of affective responses to abused substances. However because of the correlational nature of the data, it is currently not possible to determine if changes in DA release are a cause or a consequence of drug-induced hedonic change.

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Appendix 6:

Acute phenylalanine/tyrosine depletion: A new method to study the role of catecholamines in psychiatric disorders

Primary Psychiatry. 2004;11(6):XX-XX

Acute Phenylalanine/Tyrosine Depletion: A New Method to Study the Role of Catecholamines in Psychiatric Disorders

Sean P. Barrett, BA, and Marco Leyton, PhD

Focus Points

- Acute phenylalanine/tyrosine depletion (APTD) is a recently developed technique that is thought to safely, rapidly, and transiently reduce the production of the catecholamine neurotransmitters dopamine and norepinephrine in the brain.
- APTD has been shown to alter motivation, drug-related responses, and mood in healthy individuals, as well as manic symptoms in patients with bipolar disorder.
- A variation of the APTD technique may be appropriate for extended clinical use.

Abstract

The acute phenylalanine/tyrosine depletion (APTD) method was recently developed as a new tool to transiently decrease catecholamine transmission in humans. Initial studies indicate that the treatment is safe, well tolerated, and effective. Studies in primates suggest that both dopamine and norepinephrine syntheses are decreased, and that it might be possible to separate the effects of dopamine and norepinephrine using 3,4-dihydroxy-l-phenylalanine (L-DOPA). Behavioral effects appear to develop rapidly after treatment, within 3 hours in some studies. Furthermore, preliminary findings in healthy individuals suggest that APTD can lead to a mild mood-lowering effect associated with decreased interest in both natural and drug rewards. In bipolar patients, more pronounced effects may be elicited, and manic symptoms might be reduced. A variant of this technique is being developed that would be suitable for extended administration, and an initial study suggests that it could have clinical utility as a treatment augmentation strategy for hyper-dopaminergic disorders.

Introduction

The catecholamine neurotransmitters dopamine (DA) and norepinephrine (NE) are thought to contribute to the regulation of attention, arousal, mood, and motivational states.[1] Disturbances to this catecholaminergic regulation might increase vulnerability to various forms of psychopathology, including attention-deficit/hyperactivity disorder (ADHD),[2] mood disorders,[3] and substance abuse.[4] However, most of the evidence supporting these associations comes from indirect sources, such as correlations between symptoms and peripheral markers, and preclinical evidence that effective medications affect catecholamine transmission. Direct evidence for causal associations is generally sparse. One of the primary obstacles to a more direct assessment of the roles of DA and NE in psychiatric disorders has been the lack of an effective tool that safely, rapidly, and selectively decreases catecholamine function in humans. This article describes recent efforts to develop acute phenylalanine/tyrosine depletion (APTD) as a tool that might fulfill these needs.

The Catecholamine Metabolic Pathway

The synthesis of catecholamines in the brain occurs in several steps (Figure). The amino acid precursors of DA and NE, phenylalanine and tyrosine, are derived from dietary protein. Neither crosses the blood-brain barrier passively. Instead, competition for active transport into the brain occurs via a saturable system that is also used by other large neutral amino acids. Once phenylalanine and tyrosine are in the brain and taken up into catecholamine neurons, there are three enzymatic steps. First, phenylalanine hydroxylase converts the essential amino acid phenylalanine into tyrosine, thereby providing an endogenous source of the latter amino acid. Second, tyrosine hydroxylase adds a hydroxyl group to tyrosine to produce 3,4-dihydroxy-l-phenylalanine (L-DOPA). L-DOPA is then rapidly converted into DA by aromatic amino acid decarboxylase and moved into storage vesicles by the vesicular monoamine transporter. In noradrenergic neurons, these vesicles contain DA-ß-hydroxylase, the enzyme that converts DA into NE.

The conversion of tyrosine to L-DOPA is considered the rate-limit-

Mr. Barrett is a doctoral candidate in clinical psychology in the Department of Psychology at McGill University in Montréal, Canada.

Dr. Leyton is assistant professor in the Department of Psychiatry at McGill University.

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Please direct all correspondence to: Marco Leyton, PhD, Department of Psychiatry, McGill University, 1033 Pine Ave West, Montreal, Quebec, Canada H3A 1A1; Tel: 514-398-5804; Fax: 514-398-4866; E-mail: marco.leyton@mcgill.ca.

ing step in catecholamine synthesis. Tyrosine hydroxylase is the slowest of the metabolic pathway's three enzymes, and under normal physiological conditions it is incompletely saturated. As a consequence, reducing tyrosine availability should reduce catecholamine synthesis. A growing body of evidence indicates that APTD is a safe, rapid, and effective means for accomplishing this.

APTD Validation Studies

Ingestion of an amino acid load can induce protein synthesis. Since the APTD mixture lacks phenylalanine and tyrosine, these amino acids must be derived from the body's stores, resulting in a reduction in their plasma concentrations. Moreover, since APTD mixtures contain other large neutral amino acids, the competition for transport across the blood-brain barrier is also increased,[5] further reducing the amount of phenylalanine and tyrosine in the brain.[6,7]

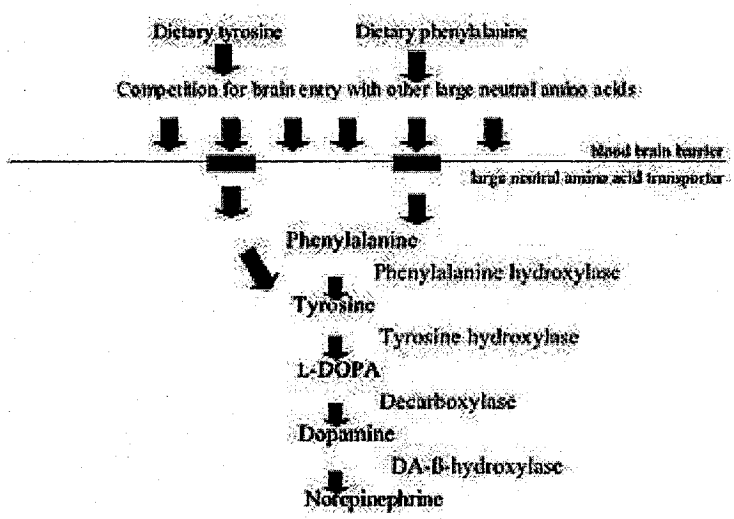
Recent studies provide compelling evidence that depletion of phenylalanine and tyrosine in the brain leads to decreased DA synthesis. In research animals, APTD decreases postmortem tissue concentrations of DA,[8] amphetamine-induced DA release,[8] cerebrospinal fluid (CSF) concentrations of the DA metabolite homovanillic acid,[9] and amphetamine- and cocaine-induced behavioral activation.[10] In humans, APTD increases circulating levels of prolactin,[11] a neuroendocrine index of decreased DA transmission, as well as [^{11}C]raclopride binding, a more direct functional neuroimaging measure of decreased DA levels in striatal synaptic clefts.[12,13] In the two positron emission tomography (PET) studies,[12,13] the APTD-induced change in [^{11}C]raclopride binding correlated with the reductions in phenylalanine and tyrosine, suggesting a direct association between DA release and precursor availability.

Less is known about the effects of APTD on NE. In nonhuman primates, APTD has been reported to decrease CSF concentrations of the NE metabolite, 3-methoxy-4-hydroxyphenethyleneglycol, to the same degree that it reduces homovanillic acid.[9] In comparison, studies in rats suggest a more selective effect on DA.[8] It remains unclear whether this reflects a difference between rodents and primates, a failure as yet to identify the locus of effect on NE, or differences in the APTD mixtures used by the two research groups. Very preliminary evidence suggests that, in humans, it may be possible to distinguish between effects of APTD that are DA versus NE mediated based on whether they are prevented by the immediate DA precursor, L-DOPA. Considering that L-DOPA may selectively increase DA synthesis,[14,15] it may reverse DA-related effects of APTD while leaving NE-related effects intact.

There are currently two different versions of the APTD mixture in use; one containing 14 amino acids,[5] and the other only 7.[8] Although these methods have yet to be directly compared, each has been successfully used to examine aspects of catecholamine functioning in humans.[12,13] Both mixtures are believed to transiently reduce catecholamine synthesis via the same mechanisms and over a similar time course.[16,17] Effects of the APTD mixtures have been observed within 3 hours of administration, and their total duration of action is thought to be <8 hours. They can therefore be used on an outpatient basis and do not require prolonged monitoring.

In addition, APTD has been demonstrated to be well tolerated in both clinical and normal human populations,[5,16] and it appears to be devoid of any serious side effects, such as the motor dyskinesia often associated with other treatments that reduce catecholamine transmission. Moreover, while numerous medications are available that bind to one or more of the multiple DA and NE receptor subtypes, these compounds tend to be nonspecific, also binding to the receptors of noncatecholaminergic transmitter systems.[18] In comparison, with the possible exception of effects on the trace amines, APTD is thought to act specifically on catecholamine synthesis and reduce transmitter binding at all DA and NE receptor subtypes.

Figure
The Catecholamine Metabolic Pathway



The catecholamine amino acid precursors phenylalanine and tyrosine are obtained from dietary sources. They compete with other large neutral amino acids for access to a saturable transporter that actively carries them across the blood-brain barrier. Once taken up into catecholamine neurons, phenylalanine undergoes two hydroxylations, first by phenylalanine hydroxylase and then by tyrosine hydroxylase, to produce 3,4-dihydroxy-l-phenylalanine (L-DOPA). L-DOPA is rapidly converted into dopamine by aromatic amino acid decarboxylase. In norepinephrine neurons, the storage vesicles contain dopamine-ß-hydroxylase, which converts dopamine into norepinephrine. The rate-limiting enzyme in catecholamine synthesis is tyrosine hydroxylase.

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Behavioral Effects of APTD in Humans

Behavioral effects of APTD are now being examined in both healthy and clinical populations (Table).[5,11,16,17,19-23] Although this is still a relatively new area of investigation, preliminary evidence suggests that APTD can affect motivation, reinforcement, and mood.

Motivation and Reinforcement

The catecholamines, particularly DA, have been implicated in various motivational processes. For example, in various laboratory animal species, DA-specific lesions interfere with appetitive behaviors directed toward normally reinforcing stimuli, including food,[24] sexual partners,[25] and abused drugs.[26] Such findings were initially interpreted as implicating DA in the pleasure associated with reward.[27] However, due largely to evidence that DA transmission is also increased during stress,[28] exploratory behavior,[29] and expectation of reward,[30] a revised view is that DA is more closely related to the motivation to interact with biologically-relevant environmental stimuli.[31] This possibility has been explored in recent APTD studies.

In healthy men and women, APTD has been reported to increase feelings of boredom[5] and apathy,[19] possibly reflecting a generalized indifference to otherwise interesting or important environmental stimuli. Consistent with this interpretation, APTD decreased the salience of rewarding cues in a decision-making task[19] and diminished the ability of the ADHD medication *d*-amphetamine to enhance responding for monetary reward.[20] The effect of APTD on reinforced learning was prevented by L-DOPA, suggesting further that it is a DA-mediated effect.[20]

Drug-Related Motivation

Animal models of addiction have long implicated DA in the addictive properties of numerous abused substances, including cocaine, amphetamine, alcohol, and nicotine.[4,26,31] Each of these substances promotes midbrain DA neurotransmission, and disruption of this action interferes with drug self-administration.[26,31] Moreover, following repeated drug exposure, environmental cues that predict drug availability gain the ability to increase DA release.[32] Preventing cue-induced DA transmission decreases drug-seeking behavior.[33] In comparison, disrupting DA transmission does not appear to diminish the hedonic effect of rewards.[31] Based on this and other evidence, it has been proposed that, in laboratory animals, DA is associated with motivational aspects of drug taking.[31]

Recent APTD findings support a role for DA in the motivational aspects of human drug-taking behavior as well. For example, APTD has been shown to decrease alcohol consumption in social drinkers[21] and cigarette craving in nicotine-dependent smokers.[17] In both cases, APTD left various aspects of drug liking unaltered, suggesting

Table
Effects of APTD on Mood and Motivational States[5,11,16,17,19-23]

Reference	Motivation/Reinforcement	Mood
Leyton, et al[5]	Increased levels of boredom	Increased depressed mood following the completion of a stressful task; no significant effect prior to challenge
Harmer, et al[11]	Not tested	Decreased "feel good" scores; no significant effect on "depressed" scores
McTavish, et al[16]	Not tested	Decreased "mind race" and "buzz" feelings following methamphetamine in healthy individuals; decreased manic symptoms in patients with bipolar disorder
Casey, et al[17]	Decreased cigarette craving but not cigarette liking; craving effect was reversed by L-DOPA	No significant mood effects reported
McLean, et al[19]	Increased apathy, decreased salience of rewarding cues in a decision-making task	Decreased "feel good" scores; increased bias for negative affect related stimuli.
Leyton, et al[20]	Decreased *d*-amphetamine enhanced responding for rewarding cues; effect was reversed by L-DOPA	Decreased subjective effects of *d*-amphetamine; effect not reversed by L-DOPA
Leyton, et al[21]	Decrease alcohol ingestion, but not alcohol liking	Not tested
McTavish, et al[22]	Not tested	Decreased "mind race" effect of *d*-amphetamine; no effect was evident prior to amphetamine challenge
Coupland, et al[23]	Not tested	No significant mood effects

APTD=acute phenylalanine/tyrosine depletion; L-DOPA=3,4-dihydroxy-l-phenylalanine.

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that the diminished motivation for drug use was independent of the enjoyment of the drug effects. The effect of APTD on nicotine craving was prevented by L-DOPA.[17] Although preliminary, these findings raise the possibility that the neurobiological substrates of drug wanting versus liking can be demarcated using the APTD method, and that DA is more closely related to the former.

Mood

In addition to their motivational effects, catecholamines have also been hypothesized to be involved in the regulation of mood. This is primarily based on observations that drugs that enhance catecholamine function tend to elevate mood, drugs that inhibit catecholamines tend to lower mood, and abnormal peripheral markers of catecholamine function are evident in patients with affective disorders.[3] Although most evidence linking catecholamines to mood remains indirect, recent APTD studies support a role for catecholamines in the mediation of positive and negative affective states. In some studies,[5,11,31] though not in all studies,[22,23] APTD has been reported to produce mild mood-lowering effects in healthy individuals. In one study,[19] subjects reported feeling less "content" and displayed a greater negative word bias in a word-response task following the ingestion of the APTD mixture, while in a second study,[11] APTD significantly decreased ratings of "feeling good."

Evidence suggests that effects of APTD on mood may be greater when there is increased demand on catecholamine function. In the one study[5] meant to explicitly assess this possibility, a depressogenic effect of APTD was seen following a stressful psychological challenge but not before it. Similarly, studies[22] suggest that APTD diminishes subjective effects of psychostimulant drugs without altering mood before drug administration.

The evidence that various "challenge" conditions might augment mood-lowering effects associated with APTD is consistent with the neurobiological data. Microdialysis studies in rodents[8] and both PET studies in humans[12,13] indicated that APTD has greater effects on DA transmission relative to resting baseline, following amphetamine administration. These findings suggest that APTD may be particularly well suited for examining psychiatric disorders characterized by hyperactive catecholamine activity while leaving normal function unaltered.

Bipolar Disorder

Indirect evidence has linked bipolar disorder with abnormalities in catecholamine functioning. For example, peripheral markers for NE functioning are increased during mania[34] and have been shown to correlate with lithium-induced changes in mood.[34] In addition, several variations of genes that code for different DA receptors have been identified as potential markers for bipolar disorder[35] and medications with known D_2 receptor antagonist actions are efficacious in treating bipolar symptoms.[35]

A recent investigation examined the effect of APTD on manic symptoms in an inpatient group of bipolar patients being treated with DA D_2 medications.[16] In this study, APTD reduced manic symptoms by approximately 35%. Because APTD effects on DA and NE were not differentiated, it is not clear if the observed effect resulted from an augmentation of the medication's D_2 effects or from a reduction in function at other DA or NE receptor subtypes. Although further work is required to delineate the precise mechanism of therapeutic action, these findings provide the first evidence that APTD can exert clinically significant effects in a psychiatric population.

Therapeutic Potential of Catecholamine Depletion

Given the evidence that APTD can acutely reduce manic symptoms and drug craving, there has been interest in developing the method for longer term administration. The original method, though, is not appropriate for long-term use. APTD requires that patients follow a strict low-protein diet so that other sources of phenylalanine and tyrosine do not become available. Moreover, because APTD induces protein synthesis and this requires phenylalanine and tyrosine from the body's remaining stores, repeated APTD administration over prolonged periods could result in malnutrition or tissue damage.

A recently developed variant of the APTD technique that is not believed to induce protein synthesis may be appropriate for long-term use.[36] It consists of an amino acid mixture containing three branched-chain amino acids (BCAAs)—leucine, isoleucine, and valine—which compete with phenylalanine and tyrosine for transport into the brain. Preliminary evidence using this technique suggests that ingestion of a BCAA mixture may exert observable effects on catecholamine transmission. For example, BCAA administration has been demonstrated to produce cognitive and endocrine effects consistent with diminished DA function in healthy humans,[36] as well as to acutely reduce manic symptoms in patients with bipolar disorder by approximately 20%.[37] This latter effect, albeit weaker than that associated with APTD, demonstrates that BCAA mixtures can exert clinically significant effects, and they may have utility for the treatment of psychiatric disorders characterized by hyperactive catecholamine activity.[16,37]

Conclusion

APTD appears to be a safe, effective, and well-tolerated method for rapidly decreasing catecholamine transmission and investigating their role in the regulation of various normal and abnormal behaviors. Preliminary APTD studies in healthy individuals support the role of catecholamines in motivational, reinforcement, and affective processes. Studies in nicotine-dependent smokers and bipolar patients suggest that APTD can decrease drug craving and manic symptoms. Although APTD does not appear to be suitable for long-term psychiatric treatment, a variation of the method does show some promise for extended therapeutic use. Potential applications of APTD and related methods include investigating the role of catecholamines in the pathogenesis and symptom expression of various psychiatric disorders, delineating the mechanisms of therapeutic drug action, augmenting treatment response in hyper-catecholamine disorders, and identifying individuals at risk. ***PP***

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Appendix 7:

Ecstasy and drug consumption patterns: A Canadian rave population study

Ecstasy and Drug Consumption Patterns: A Canadian Rave Population Study

Samantha R Gross, PhD(c)[1], Sean P Barrett, PhD(c)[2], John S Shestowsky, PhD(c)[2], Robert O Pihl, PhD[3]

Objective: This study investigates the drug consumption patterns of a sample of rave attendees in the city of Montreal, Quebec, and seeks to identify the prevalence of 3,4-methylendioxymethamphetamine (MDMA) and other drug use in this population.

Method: We administered a self-report questionnaire to 210 respondents. For various licit and illicit substances, participants reported their age of first use, number of lifetime uses, and usage in the previous 30 days.

Results: We found a significant rank order for the sequence of first use: 1) alcohol, 2) nicotine, 3) cannabis, 4) LSD, 5) psilocybin, 6) amphetamine, 7) cocaine, 8) MDMA, 9) gamma-hydroxybutyrate (GHB), 10) ephedrine, 11) ketamine. Alcohol and cannabis were the most commonly used substances, both in cumulative number of lifetime uses and in usage in the preceding 30 days. MDMA and amphetamine were also notable as the next 2 most popular drugs for use in the preceding 30 days and in terms of those who had tried the drugs at least once. We identified a progressive rank order of experimentation, with early alcohol or cannabis use (or both) associated with the early use of all other drugs tried by more than 25% of the sample. We found MDMA and amphetamine use to be prevalent, as was general experimentation with all drugs studied, other than heroin.

Conclusion: Drug consumption levels were substantial in this "rave" population, particularly with respect to recent use of MDMA, amphetamine, cannabis, and alcohol. Results also indicate that the sequence of drug experimentation in this population follows an identifiable pattern.

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See page 550 for research funding and support and page 551 for author affiliations.

Clinical Implications

- This is the first study to identify the drug-use patterns and histories of individuals attending Canadian raves.
- A progression of drug use has been identified.
- These findings could be used to target specific at-risk individuals in prevention programs.

Limitations

- This study relied on retrospective self-report data.
- The sample size was moderate.
- The sample was self-selected.

Key Words: *ecstasy, 3,4-methylendioxymethamphetamine, MDMA, polydrug use, rave, alcohol, cannabis, amphetamine*

Beginning in the late 1980s, a new "rave" subculture emerged. It was characterized by all-night technodance parties and the use of illicit drugs, particularly 3,4-methylendioxymethamphetamine (MDMA; also known as "ecstasy," "E," "X," and "XTC"). Originating in Great Britain, the trend for youth to attend these parties became strong in Canada around 1991 and has reportedly been growing exponentially ever since, as has an overall increase in MDMA use

(1,2). Despite these increases, very little is known about the overall drug-use patterns of individuals who attend raves and how these patterns relate to MDMA use.

MDMA is classified as an empathogen or enactogen (3) because the subjective experience has been described as intensely emotional and as creating the perception that one can experience the emotions of others (4). Users typically report the impression of feeling clear-headed, serene, euphoric, and sensual; significant visual illusions common to LSD and other psychedelics generally do not occur (4–6).

As recently as 1986, some physicians believed ecstasy to be a safe drug (7). However, recent research has revealed many negative effects associated with ecstasy use. Acute adverse effects include restlessness, ataxia, tremor, myoclonus, diarrhea, and the most severe side effect, hyperthermia (8). MDMA use has been associated with sudden death and cardiovascular collapse (9), with the most common cause of death being hyperthermia (10). The behavioural and environmental factors that often coexist with MDMA consumption (for example, concomitant ingestion of other illicit drugs and high ambient temperature) may increase the risk for severe adverse effects, particularly cardiovascular complications and hyperthermia. Prolonged exercise (for example, dancing), high ambient temperatures, and high humidity are typical in rave and club environments and are believed to potentiate the neurologic toxicity of MDMA (11,12). Indeed, in the US emergency room visits related to MDMA consumption have increased from 637 in 1997 to 1143 in 1998 (13).

The possible long-term consequences of MDMA use have also generated concern. It has been reported that repeated administration of MDMA in laboratory animals diminishes serotonin and dopamine levels and damages the nerve terminals from which serotonin is released, in a dose-related manner and with incomplete recovery (14–17). With some controversy, many researchers nonetheless regard animal studies on MDMA to be relevant to human use. For example, the finding that the loss of serotonergic (5-HT) axons in monkeys is greater than in rats given a fourfold greater dosage of MDMA has led some to conclude that MDMA is potentially far more neurotoxic in primates than in nonprimate mammals (18).

According to the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), recent use is higher for ecstasy than for amphetamines and LSD (19). Although similar results have been reported in the US (20), very little is known about the patterns of MDMA consumption in Canada. While some general surveys have identified illicit drug-use patterns of high school students (21–24), university students (25,26), and university athletes (27), none have targeted individuals who attend rave parties—individuals thought to be at greater risk for MDMA use.

The Centre for Addiction and Mental Health (CAMH) produced a study that surveyed 7800 university students across Canada (25). This study identified 10.2% of the population as using illicit drugs other than cannabis. Alcohol was noted as the drug of choice among university students, with 92% of the population having tried it at least once. Quebec students had the highest rate of both cannabis and alcohol use in the previous 12 months (28.7% and 88.3%, respectively). MDMA was reportedly used by 4% of the entire sample; in accordance with the EMCDDA study (19), this reveals the greatest prevalence for lifetime use, compared with drugs other than cigarettes, cannabis, or alcohol. Although the prevalence of ecstasy use might not appear to be salient, it comprises a substantial proportion of the 10.2% trying any drug other than alcohol or cannabis. Another series of surveys was conducted by Parent Resources Institute for Drug Education (PRIDE) every other year between 1987 and 1992. These studies surveyed students in grades 6 through 12 and found that 14.1% of the population used cannabis in 1991–1992, while 5.7% of the population used hallucinogens (21,22). While such surveys indicate the usage of an age group similar to that assumed to attend rave parties, a sequence of experimentation has yet to be identified in Canada. Australian and European studies have, however, identified the progression or patterns of drug use. The following drug-use sequence was found in a survey of 10 812 students in Norway (aged 14 to 17 years): 1) alcohol, 2) cigarettes, 3) cannabis, 4) amphetamines, 5) ecstasy, and 6) heroin (28). This study suggested that adolescents with a pattern of polydrug use have used ecstasy and that ecstasy is significantly associated with attendance at house parties and with subcultural music preferences. In Australia, studies of rave populations found that 90% of attendees had tried LSD, 76% had tried ecstasy, and 69% had tried amphetamine (29). The researchers noted that LSD is a possible sequential gateway drug to other substances and indicated the popularity of both ecstasy and amphetamines among rave attendees.

Our study aimed to delineate the drug consumption histories of those attending raves in Montreal, Canada, and to determine whether these are similar to the histories found elsewhere. In addition, we attempted to determine the popularity of MDMA in this group and to identify potential specific sequences of drug experimentation within samples of rave-attending individuals.

Table 1 Drug consumption in Canadian youth attending raves

Drug	Respondents ever using (%)	Age of first use Mean (SD)	Estimated number of lifetime uses Mean (SD)	Users consuming in preceding 30 days (%)	Number of uses in preceding 30 days
Alcohol	89.5	14.1 (2.2)	361.2 (828.6)	68.7	9.3 (13.2)
Amphetamine	73.3	18.5 (3.1)	52.6 (268.3)	64.9	2.3 (2.0)
Cannabis	91.4	15.1 (2.6)	1068.4 (388.0)	67.7	23.6 (26.6)
Cocaine	34.8	18.6 (2.7)	23.2 (46.0)	27.4	2.0 (1.8)
Ephedrine	21.0	20.2 (3.8)	167.2 (667.5)	31.8	19.9 (38.6)
GHB	18.6	19.7 (2.8)	6.1 (18.22)	28.2	3.6 (5.7)
Heroin	3.8	19.6 (3.6)	43.3 (82.5)	0.0	0.0 (0.0)
Ketamine	13.8	20.2 (3.5)	5.5 (8.93)	33.5	1.2 (0.4)
LSD	66.2	16.3 (2.7)	63.6 (317.2)	12.7	1.7 (1.4)
MDMA	65.2	19.3 (3.4)	27.4 (52.3)	53.2	1.9 (1.9)
Nicotine	64.3	14.2 (2.3)	NA	NA	NA
Psilocybin	70.0	16.5 (2.9)	22.5 (45.1)	22.1	1.7 (0.9)

GHB = Gamma-hydroxybutyrate
MDMA = 3,4-methylenedioxymethamphetamine

Method

Participants ($n = 210$) were recruited from 3 different raves in Montreal, a bilingual metropolitan Canadian city ($n = 48$, $n = 64$, $n = 98$, respectively). The 3 events were all large-scale (3000 to 10 000 people) and held indoors at private venues. Events similar in size and type are frequently held in other large Canadian metropolitan areas. Subjects were randomly approached by 3 research associates and asked to complete an anonymous self-report questionnaire for a scientific investigation. Participants were informed that their responses would remain strictly confidential and that their participation was strictly voluntary. The questionnaire, conducted in both English and French, was based on an abbreviated version of the Addiction Severity Index (ASI) (30), modified to incorporate drug classes not included on the original index. At the first 2 events, participants were asked to identify age of first use, number of lifetime uses, and number of uses in the past 30 days for 11 different substances. Information was collected on alcohol, heroin, marijuana, amphetamine, ephedrine, cocaine, LSD, psilocybin, ketamine, gamma-hydroxybutyrate (GHB), and MDMA use. At the third rave, a question regarding the age of first use of nicotine was added to the survey.

Results

Questionnaires were completed by 80 women (38.8%) and 126 men (61.2%), with 4 participants not indicating their sex. Statistical analyses were based on 11 of the drugs surveyed; we omitted heroin because only 8 respondents had used it. Participant ages ranged from 16 to 32 years (mean 21.4 years, SD 3.18). In all analyses, we considered sex and event attended; however, no significant interaction effects were found. Drug histories are summarized in Table 1.

Progression of Drug Use

Average age of first use for alcohol was 14.05 years (SD 2.18, $n = 188$), for cannabis 15.13 years (SD 2.59, $n = 192$,) and for nicotine 14.21 years (SD 2.34, $n = 63$), which identified these drugs as potentially the first 3 steps in drug experimentation (see Table 1).

To accommodate the data that fit a block design with missing values, we used a univariate analysis of variance to calculate significant differences between the means of age of first use. We treated subjects independently to account for variability in the number of different drugs used by each participant. We found an overall significant difference between mean age of first use and the particular drug used ($F = 60.125$, $P < 0.001$). We than applied Bonferroni and Tukey honestly significant difference (HSD) contrasts to identify specific significant mean differences. We found significant mean differences with the following subsets, defined using harmonic mean sample sizes and an alpha level of 0.05: 1) alcohol, nicotine, and cannabis; 2) cannabis, LSD, and psilocybin; 3) amphetamine, cocaine, MDMA, GHB, ephedrine, and ketamine. Based on overall significance, a rank order for progression can be inferred, which indicates the following linear trend in progression of first use: 1) alcohol, 2) nicotine, 3) cannabis, 4) LSD, 5) psilocybin, 6) amphetamine, 7) cocaine, 8) MDMA, 9) GHB, 10) ephedrine, and 11) ketamine.

To test for linear and quadratic trends, we also applied a repeated-measures analysis of variance (ANOVA) to the data on drugs used by more than 25% of the sample. While this analysis yields results only for those subjects who used all the

listed substances ($n = 44$), we found a similarly significant linear trend for the experimentation order: 1) alcohol, 2) cannabis, 3) LSD, 4) psilocybin, 5) amphetamine, 6) cocaine, 7) MDMA ($F = 304.8$, $P < 0.001$). To further delineate these trends, we employed a correlational analysis using the nonparametric Spearman's rho to account for monotonic relations between variables. We found significant positive correlations at the 0.01 level between the age of first use of alcohol and cannabis, cocaine, amphetamines, ephedrine, GHB, psilocybin, MDMA, nicotine, and LSD. As well, we found significant positive correlations between age of first use of cannabis and age of first use of all drugs except ketamine. After we applied a Bonferroni correction, significant relations were maintained for all except the alcohol-to-amphetamine, -ephedrine and -GHB correlations and the cannabis-to-GHB and -ephedrine relations.

Total Number of Lifetime Uses

Table 1 indicates the percentage of the subjects who had used each drug.

Although mean computations suggest the highest use for cannabis (mean 1088.4) and alcohol (mean 361.2), it is important to note that we did not collect lifetime estimates of tobacco consumption. When median scores are calculated to account for outliers in the data, alcohol (median 100) and cannabis (median 150) remain the most frequently used substances.

We conducted bivariate correlations using the nonparametric Spearman's rho to determine relations among the number of lifetime uses for different drug types. After we applied a Bonferroni statistical correction, we found significant relations ($P < 0.01$) for the following groupings: alcohol lifetime use correlated with cannabis lifetime use; amphetamine lifetime use with MDMA lifetime use; cannabis lifetime use with psilocybin lifetime use; and LSD lifetime use with psilocybin lifetime use.

Number of Uses in Preceding 30 Days

Table 1 reports what percentage of subjects who had reported at least 1 use of a particular drug had used that drug in the preceding 30 days, as well as the mean number of uses for each drug during this time period. Listed in descending order according to percentage of recent recurrent users, the drugs rank as follows: alcohol, cannabis, amphetamine, MDMA, ketamine, ephedrine, GHB, psilocybin, and LSD.

Median scores were also considered, to account for extreme users. With these scores, cannabis is notable as the most frequently consumed drug during the preceding 30 days (median 15), followed by alcohol (median 5).

Discussion

Our study sought to clarify the drug-consumption patterns of Montreal youth who attend raves. Research on this population suggests that rave attendees represent a significant proportion of illicit drug users. Our findings confirm that members of this group take greater quantities and experiment with a greater variety of substances than do their peers who do not attend raves (21–27).

To determine whether there was a general pattern of stepwise drug experimentation, we applied 2 different statistical analyses to the data. We identified the following progressive pattern: 1) alcohol, 2) nicotine, 3) cannabis, 4) LSD, 5) psilocybin, 6) amphetamine, 7) cocaine, 8) MDMA, 9) GHB, 10) ephedrine, and 11) ketamine. It is notable that the substances used by more than 10% but less than 25% of this population appeared as the last 3 in the sequence of experimentation. A similar study in Norway determined the following best-fit for the progression pattern: 1) alcohol, 2) cigarettes, 3) cannabis, 4) amphetamines 5) ecstasy, and 6) heroin (28). Despite the fact that this was a normal population survey, and questions on hallucinogen use were not incorporated, the overall similarities with our findings are striking.

The sample used alcohol and cannabis substantially. Overall, 89.5% of the subjects reported prior intoxication with alcohol, 69.7% of these in the past 30 days. Similarly, 91.4% of those surveyed reported having used cannabis, 67.7% of these in the previous 30 days. Interestingly, the early use of either substance was associated with an early use of cocaine, psilocybin, LSD, and MDMA, suggesting their potential as possible "gateway" drugs.

While MDMA was the third most commonly used drug in this sample, the age of first use appeared later (that is, 8th) in the drug experimentation sequence than had been anticipated. As well, the lifetime uses and uses in the preceding 30 days were also lower than had been expected. MDMA, however, is still among the most prevalent drugs consumed at raves. Indeed, the high prevalence of MDMA use found in this study is consistent with research findings in rave samples surveyed in Australia (76%) (29). Since rave events typically occur on weekends, however, occasion to take MDMA may be regarded as less frequent than occasion for consuming substances such as alcohol or cannabis.

The prevalence of amphetamine use, including both recent and overall consumption, was comparable to that of MDMA. It was the third most popular drug for use in the preceding 30 days: 47.6% of those surveyed reported amphetamine use,

slightly exceeding the 40% reporting MDMA use during this period. Further, while 73.3% of the overall sample reported ever using amphetamine, a comparable 75.2% reported MDMA lifetime use. These findings suggest that, in addition to MDMA, amphetamine should be examined as a primary drug used by rave populations.

The use of the hallucinogenic drugs LSD and psilocybin was also reported by a substantial portion of the sample (56.2% and 70%, respectively). Although participants reported initially experimenting with these drugs at a relatively early age, most users did not report consuming them in the preceding 30 days (22% reported pilocybin use, and 12.7% reported LSD use). These findings suggest that while the use of hallucinogenic drugs often precedes the consumption of drugs like MDMA and amphetamine, these drugs are seldom in active use by individuals attending raves. It is interesting to note that while the level of LSD use was positively associated with the level of psilocybin consumption, using these drugs did not reliably predict the subsequent level of MDMA or amphetamine use, suggesting a limited role for hallucinogens as gateway drugs in a rave population.

Several drugs, including ketamine, GHB, and ephedrine, did not surface as popular substances within this sample, each having been used by fewer than 25% of those surveyed. Nevertheless, approximately one-third of those who had experimented with these drugs had done so recently. It seems plausible that the apparent infrequent use of these 3 drugs is related to their late introduction into the typical sequence of drug experimentation.

Although this study identifies the drug-consumption patterns and histories of individuals who attend Montreal-area raves, it is appropriate to address some of the investigation's possible limitations. Because this study relied on retrospective recall, the accuracy of such reports might be questioned. However, it should be noted that the research question precludes prospective data collection and that the methods used are in accord with abundant published reports that use a similar methodology (for example, 27–29). In addition there are several indications that substance use self-report data can be both reliable and valid (for example, 30,31).

A second issue involves the degree to which this moderate sample can accurately reflect the drug-taking patterns of Montreal rave attendees in general. Because the participants were self-selected for this investigation, it is possible that they do not represent the group as a whole. Although we attempted to minimize this by administering questionnaires at 3 separate events and found no significant differences among these subgroups, only a random sample of rave attendees would ensure the generalizability of these findings. Nevertheless, the present results are consistent with findings obtained from other samples of drug users (for example 28,29). As well, since an entire generation of ages was surveyed (range 16 to 32 years), this study potentially captured both long-term and relatively new partygoers.

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[1]Doctoral Candidate, National Addiction Centre, Institute of Psychiatry, Kings College, London, UK.
[2]Doctoral Candidate, Department of Psychology, McGill University, Montreal, Quebec.
[3]Professor, Department of Psychology, McGill University, Montreal, Quebec.
Address for correspondence: SP Barrett, 1205 Dr Penfield, Department of Psychology, McGill University, Montreal, QC H3A 1B1
e-mail: barrett@ego.psych.mcgill.ca

Résumé : L'ecstasy et les modèles de consommation de drogues : une étude de la population canadienne des raves

Objectif : Cette étude examine les modèles de consommation de drogues d'un échantillon de participants à un rave à Montréal, au Québec, et cherche à déterminer la prévalence de la 3, 4 - méthylènedioxyamphétamine (MDA) et de l'utilisation d'autres drogues au sein de cette population.

Méthode : Nous avons administré un questionnaire d'auto-évaluation à 210 répondants. En ce qui concerne diverses substances légales et illégales, les participants ont déclaré l'âge de leur première utilisation, le nombre d'utilisations à vie et l'utilisation dans les 30 jours précédents.

Résultats : Nous avons trouvé un rang significatif dans la séquence de première utilisation : 1) alcool, 2) nicotine, 3) cannabis, 4) LSD, 5) psilocybine, 6) amphétamine, 7) cocaïne, 8) MDA, 9) gamma-hydroxybutyrate (GHB), 10) éphédrine, 11) kétamine. L'alcool et le cannabis étaient les substances les plus fréquemment utilisées, tant en nombre cumulatif d'utilisations à vie qu'en nombre d'utilisations dans les 30 jours précédents. La MDA et l'amphétamine étaient également mentionnées comme étant les deux drogues dont l'utilisation venait en deuxième dans les 30 jours précédents et pour ceux qui avaient essayé les drogues au moins une fois. Nous avons repéré un ordre d'expérimentation progressif, soit une première utilisation d'alcool ou de cannabis (ou des deux) associée avec une première utilisation de toutes les autres drogues essayées par plus de 25 % de l'échantillon. Nous avons constaté la prévalence de l'utilisation de la MDA et de l'amphétamine, et de l'expérimentation générale de toutes les autres drogues à l'étude, autres que l'héroïne.

Conclusion : Les niveaux de consommation de drogues étaient substantiels chez cette population de « raves », en particulier en ce qui concerne l'utilisation récente de MDA, d'amphétamine, de cannabis et d'alcool. Les résultats indiquent également que la séquence d'expérimentation des drogues chez cette population est conforme à un modèle identifiable.

Appendix 8:

Ethics certificates and permissions